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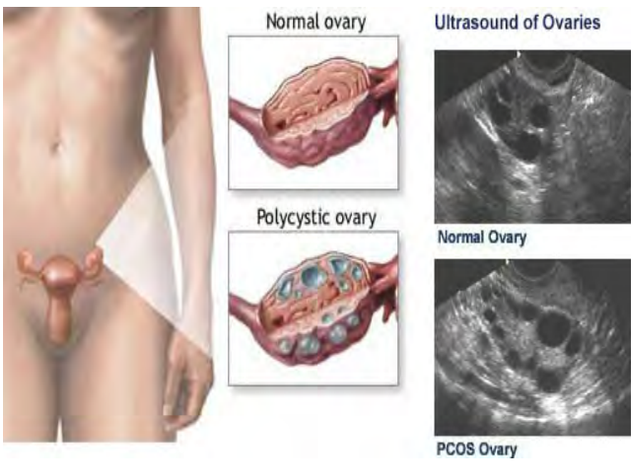
The effect of clomiphene citrate as the first-line treatment of infertile women with polycystic ovarian syndrome (PCOS) in fetal sex: a clinical trial

Athar RJ, Azadeh M, Jahromi Mojtaba RZ, Soolmaz P, Mohamadali N, Kalani N.



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T.:+90 3128761089, E-Mail: info@jcam.com.tr

Editor
Orhan Yücel

GATA Göğüs Cerrahisi. AD. 06118, Etlik, Ankara Turkey.
T.:+905303042583, E-Mail: editor@ jcam.com.tr

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National Editorial Board

Table of Contents

A. Original Research

Is glucose tolerance test an appropriate predictive marker in screening of gestational diabetes mellitus?

Glucose tolerance

Athar Rasekhjahromi[1], Marjan Jaladat[2], Nazanin Davari[2], Masoud Ghaneeijahromi3, Zahra Zarei Babaarabi[1], Navid Kalani[1]
[1]Women's Health and Disease Research Center, [2]General Practitioner, Student of Research Committee,
[3]Anesthesiology, Critical Care And Pain Management Research Center,
Jahrom University of Medical Sciences, Jahrom, Iran

Abstract

Aim: Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance developed during pregnancy it is a significant danger to both fetus and the pregnant woman, so it should be diagnosed as soon as possible to reduce its related maternal and fetal complications. An early diagnosis highly depends on appropriate screening tests. The purpose of this study is to evaluate the sensitivity of glucose tolerance test in the screening of Gestational diabetes mellitus(GDM). Material and Method: This study was conducted on 460 pregnant women between 24 and 28 weeks of gestations. All the pregnant women underwent 50-g glucose challenge test as our routine screening protocol. Pregnant women with a positive GCT underwent 3-hour 100-g OGTT within seven days. Pregnant women who had normal GTT were followed up with FBS and 2-hour blood sugar in 2 weeks later. The FBS value of 105 mg/dl and the 2hour blood sugar value of 120 mg/dl are accepted as the threshold value for GDM). Results: Based on FBS, the sensitivity of OGTT in the diagnosis of GDM is 66.67%, and due to adverse effects of high glucose on both mother and fetus, this is not a good screening test, and we have to find a better way for screening of GDM. Discussion: We found that patients with abnormal GCT and normal OGTT results are at risk of GDM and maternal and fetal complications. Finally, we should consider the group of women with an abnormal GCT result, but normal OGTT result, to be a high-risk pregnancy group.

Keywords

Diabetes Mellitus; Sensitivity, Predictive Marker; GCT; OGTT

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Corresponding Author: Athar Rasekhjahromi, Women's Health and Disease Research Center, Jahrom University of Medical Sciences, Jahrom, Iran.
E-Mail: Drrasekh@yahoo.com

Introduction

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance developed during pregnancy, and it is associated with fetal and maternal risk [1]. It's a worldwide increasing phenomenon which involved about 15% of pregnant women [2]. GDM is a significant danger to both fetus and the pregnant woman [3]. Identifying women with GDM is important during early pregnancy

to minimize maternal and neonatal morbidity [4]. Improving screening tests is important for early detection and subsequently timely intervention [5]. GDM is screened by administration of a 50-g, 1-hour glucose challenge test (GCT) between 24 and 28 weeks of gestation, if the GCT result is abnormal, then screening is followed by the administration of a 100-g, 3-hour oral glucose tolerance test (OGTT) to confirm the diagnosis [6]. Ravi Retnakaran et al. showed that an abnormal GCT, even in the presence of normal OGTT, is associated with abnormalities in postpartum metabolic function and can lead to both glycemia and beta-cell dysfunction at 3-months postpartum, they also mentioned that these women have a higher risk of cardiovascular disease over 12.3 years of median follow-up [7].

Munira Dudhbhai et al., in the study of characteristics of patients with abnormal glucose challenge test and normal oral glucose tolerance test showed different maternal characteristics and backgrounds compared with patients in whom both test results were normal. They revealed an increased likelihood for the development of overt diabetes mellitus later in life [8].

Authors in a study compared characteristics of patients who had abnormal glucose challenge test and normal oral glucose tolerance test results with normal and gestational diabetic patients, they showed that women who failed the GCT, but not the OGTT and thus did not receive the diagnosis of GDM are still at risk of delivering a macrosomic infant [9].

At present, the status of carbohydrate metabolism in pregnant women with high glucose levels, which exceeds the critical threshold value of GCT, but normal 100-g 3-hour OGTT is not clearly evaluated.

The purpose of this study is to evaluate the sensitivity of glucose tolerance test in the screening of Gestational diabetes mellitus(GDM) in Dr. Rasekh's clinic dependent to Jahrom university of medical science, Iran.

It should be noted that universal agreement on the optimal screening protocol and diagnostic criteria for GDM is lacking [10].

Material and Method

This diagnostic study was conducted from January 2015 to December 2015 on 460 pregnant women referred to Dr. Rasekh clinic between 24 and 28 weeks of gestation in Jahrom city, Iran.

Gestational age was calculated based on last menstrual period and according to a reliable menstrual history confirmed by ultrasonography before 20 weeks of gestation.

All the pregnant women underwent 50-g glucose challenge test as our routine antenatal screening protocol. Fifty grams of glucose was administered orally regardless of day, time or the fasting state.

Venous plasma glucose was measured at the first hour of the glucose load. A plasma glucose value of 130 mg/dL is accepted as the threshold value for the positive glucose challenge test.

Pregnant women with a positive challenge test underwent 3-hour 100-g OGTT within seven days. Blood samples were taken at 8:00 am after 12-hours fast and at 60, 120 and 180 minutes following the 100-g oral glucose load. Plasma glucose levels were measured by hexokinase method using Olympus autoanalyser. (Olympus Diagnostica GmbH-Irish Branch-Lismeehan).

At least two plasma glucose levels exceeding the cut-off values following OGTT were essential for the diagnosis of GDM.

Inclusion criteria in this study were a single pregnancy and a pregnancy between 24 and 28 gestational weeks.

Exclusion criteria included: pregnant women with an abnormal blood sugar in GTT, pregnant women who had diabetes mellitus before pregnancy and those who had an infectious, cardiovascular or coagulative disease or other underlying diseases.

Pregnant women who had normal GTT were followed up with FBS and 2-hour glucose challenge test in 2 weeks later. The FBS value of 105 mg/dl and the 2HPP value of 120 mg/dl are accepted as the threshold value for GDM (Gestational diabetes mellitus).

Assessment method

The follow-up of the cases were performed by a gynecologist in Dr. Rasekh clinic in Jahrom city, Iran.

Results

The subjects with abnormal GCT were 122 pregnant women who were assessed by OGTT, and the women with normal OGTT were followed up with FBS and 2hr BS in 2 weeks later. The subjects were divided into four groups:

a= 20: pregnant women with abnormal GTT and abnormal FBS or 2 hr BS.

b= 0: pregnant women with abnormal GTT but normal FBS or 2 hr BS.

c= 10: pregnant women with normal GTT but abnormal FBS or 2hr BS who have gestational diabetes in the follow-up.

d= 92: women with normal GTT and normal FBS who didn't have gestational diabetes in the follow-up.

The sensitivity of OGTT in the diagnosis of GDM based on FBS is 66.67 %, and due to the adverse effect of high glucose on both mother and fetus, this is not a good screening test, and we have to find a better way for screening of GDM.

Discussion

The diagnosis of GDM is confirmed if more than two values of GTT is abnormal [11]. Our results showed that the pregnant women with abnormal GCT and normal GTT are at risk of GDM. A few studies also have shown that pregnant women with positive GCT but normal OGTT are still at increased risk of the adverse perinatal outcome [12].

Langer et al. also revealed that treatment of pregnant women with borderline glucose intolerance leads to less maternal and fetal complications [13]. Gezer et al. have suggested that the pregnant women who were screened for GDM and had a normal GTT result are predisposed to obstetric complications related to the glucose intolerance [14]. Mello et al. also have shown

that the patients with abnormal GCT results and subsequently normal GTT are prone to have macrocosmic infants [15]. Authors in another study showed that one step screening test might decrease the rate of macrosomia [16]. The findings of these studies support our results.

Although guidelines have shown that screening of GDM is based on 100 g, 3-hour oral glucose tolerance test (OGTT) which confirms the diagnosis of GDM, the studies were done on the screening of GDM have shown that GDM screening tests might have a low sensitivity and specificity [17].

R Bhat et al. in a study conducted in 2005 mentioned that Patients with abnormal glucose challenge test (GCT) and normal oral glucose tolerance test (OGTT) are also at increased risk for complications, such as macrosomia and pre-eclampsia [18].

Researchers in another study found that GCT lacks specificity (41.8%) and they believed that diagnosis of GDM by OGTT based on initial GCT screening leaves 21.5% undiagnosed and they suggest a single glucose challenge test with 75 g of oral glucose load and diagnosing GDM if 2 hour PPG is > 140 mg/dL as WHO recommended [19].

On the other hand, some authors have focused on HbA1C as determining factor in the screening of GDM [20,21,22,23]. The hemoglobin A1C test is frequently used to evaluate long-term glucose control in diabetics [24].

Paula Breitenbach Renz et al. have shown that combined HbA1c and OGTT measurements may be useful in diagnosing GDM [25].

In a recently published study, researchers found that a HbA1C score of 5.45% or more had a sensitivity of 86% and a specificity of 61% for gestational diabetes. However, HbA1C can be useful for the screening of GDM but its specificity is somewhat low, and more research is needed before it can be routinely recommended.

Table 1. Classification of patients

Patients number in each group	GTT	FBS
20	abnormal	abnormal
0	abnormal	normal
10	normal	Abnormal
92	normal	Normal

Results

Diagnostic or Screening Test Evaluation

Single Table Analysis

	Positive	Negative	Total
Positive	20	0	20
Negative	10	92	102
	30	92	122

Parameter	Estimate	Lower - Upper 95% CIs	Method
Sensitivity	66.67%	(48.78, 80.77)	Wilson Score
Specificity	100%	(95.99, 100)	Wilson Score
Positive Predictive Value	100%	(83.89, 100)	Wilson Score
Negative Predictive Value	90.2%	(82.89, 94.59)	Wilson Score
Diagnostic Accuracy	91.8%	(85.57, 95.49)	Wilson Score
Likelihood ratio of a Positive Test	'undefined'	('?' - 'undefined')	
Likelihood ratio of a Negative Test	0.3333	(0.274 - 0.4055)	
Diagnostic Odds	'undefined'	('?' - 'undefined')	
Cohen's kappa (Unweighted)	0.751	(0.5792 - 0.9229)	
Entropy reduction after a Positive Test	'?'%		
Entropy reduction after a Negative Test	23.7%		
Bias Index	-0.08197		

Conclusion

We found that patients with abnormal GCT and normal OGTT results are at risk of GDM and maternal and fetal complications. Finally, the group of women with an abnormal GCT result, but subsequently normal OGTT result should be considered to be a high-risk pregnancy group. This group has more tendency of overt diabetes mellitus later in life. The sensitivity and specify of GDM screening tests Also should be increased.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

Declaration of interest

The authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

References

1. Price LA. Awareness of Gestational Diabetes and its Risk Factors among Pregnant Women in Samoa. Hawaii Journal of Medicine and public healt. Lucy Anne 2007;76(2):48–54.

2. Fatima SS, Rehman R, Alam F, Madhani S, Chaudhry B, Khan TA. Gestational diabetes mellitus and the predisposing factors. J Pak Med Assoc. 2017; 67(2):261-265.

3. Ostadrahimi A, Mohammad-Alizadeh S, Mirgafourvand M, Yaghoubi S, Shahrisa E, Farshbaf-Khalili A. Effects of Fish Oil Supplementation on Gestational Diabetes Mellitus (GDM): A Systematic Review. Iran Red Crescent Med J. 2016;18(11):e24690.

4. Kumru P, Arisoy R, Erdogdu E, Demirci O, Kavrut M, Ardıc C. Prediction of gestational diabetes mellitus at first trimester in low-risk pregnancies. Taiwanese Journal of Obstetrics & Gynecology. 2016;55(6):815-20.

5. Brink HS, Alkemade M, van der Lely AJ, van der Linden J. Investigating screening for diabetes in women with a history of gestational diabetes. The Netherlands Journal of Medicine. Neth J Med. 2016;74(10):429-33.

6. Nicklas JM, Zera CA, Lui J, Seely EW. Patterns of gestational diabetes diagnosis inside and outside of clinical guidelines. BMC pregnancy childbirth. BMC Pregnancy Childbirth. 2017;17(1):11.

7. Retnakaran R, Qi Y, Sermer M, Connelly PW, Hanley AJG, Zinman B. An Abnormal Screening Glucose Challenge Test in Pregnancy Predicts Postpartum Metabolic

Dysfunction, Even When the Antepartum Oral Glucose Tolerance Test is Normal. PMC Canada Author manuscripts. Clin Endocrinol (Oxf). 2009; 71(2):208–14.
8. Dudhbhai M, Lim L, Bombard A, Juliard K, Meenakshi B, Trachelenberg Y, et al. Characteristics of patients with abnormal glucose challenge test and normal oral glucose tolerance test results: Comparison with normal and gestational diabetic patients. Am J Obstet Gynecol. 2006;194(5):42-5.
9. Mello G, Parretti E, Mecacci F, Lucchetti R, Cianciulli D, Lagazio C, et al. Anthropometric characteristics of full-term infants: effects of varying degrees of "normal" glucose metabolism. J Perinat Med 1997;25:197-204.
10. Moses RG, Cheung NW. Point: universal screening for gestational diabetes mellitus. Diabetes Care. 2009;32(7):1349-51
11. Rani PR, Begum J. Screening and Diagnosis of Gestational Diabetes Mellitus, Where Do We Stand. J Clin Diagn Res. 2016;10(4):1-4.
12. Sermer M, Naylor CD, Farine D, Kenshole AB, Ritchie JW, Gare DJ, et al. The Toronto Tri-Hospital Gestational Diabetes Project. A preliminary review. Diabetes Care 1998;21(Suppl 2): 33-42
13. Langer O, Brustman L, Anyaegbunam A, Mazze R. The significance of one abnormal glucose tolerance test value on adverse outcome in pregnancy. Am J Obstet Gynecol 1987;157(3):758-63.
14. Gezer A, Esen F, Mutlu H, Ozturk E, Ocak V et al. Prognosis of patients with positive screening but negative diagnostic test for gestational diabetes. Arch Gynecol Obstet 2002; 266(4):201-4.
15. Mello G, Parretti E, Mecacci F, Lucchetti R, Cianciulli D, Lagazio C, et al. Anthropometric characteristics of full-term infants: effects of varying degrees of "normal" glucose metabolism. J Perinat Med 1997;25(2): 197-204.
16. Seshiah V, Balaji V, Balaji MS, Sekar A, Sanjeevi CB, Green A. One step procedure for screening and diagnosis of gestational diabetes mellitus. J Obstet Gynecol India. 2005, 55(6):525-29.
17. Mohan V, Mahalakshmi MM, Bhavadharini B, Maheswari K, Kalaiyarasi G, Anjana RM et al. Comparison of screening for gestational diabetes mellitus by oral glucose tolerance tests done in the non-fasting (random) and fasting states. Acta Diabetol. 2014;51(6):1007-13
18. Bhat R, Venkatesh D, Kumar P. Influences of One Elevated Glucose Tolerance Test Value on Pregnancy Outcome. The Internet Journal of Gynecology and Obstetrics. 2005;6(1):1-4.
19. Seshiah V, Balaji V, Balaji MS, Sekar A, Sanjeevi CB, Green A. One step procedure for screening and diagnosis of gestational diabetes mellitus. J Obstet Gynecol India. 2005, 55(6):525-29.
20. Odsæter IH, Åsberg A, Vanky E, Mørkved S, Stafne SN, Salvesen KA et al. Hemoglobin A1c as screening for gestational diabetes mellitus in Nordic Caucasian women. Diabetology & Metabolic Syndrome. 2016;8:43.
21. O'Shea P, O'Connor C, Owens L, Carmody L, Avalos G, Nestor L, et al. Trimester-specific reference intervals for IFCC standardized hemoglobin A(1c): new criterion to diagnose gestational diabetes mellitus (GDM)? Ir Med J. 2012;105(5 Suppl):29–31.
22. Rajput R, Yogesh Y, Rajput M, Nanda S. Utility of HbA1c for diagnosis of gestational diabetes mellitus. Diabetes Res Clin Pract. 2012; 98: 104–7.
23. Sevket O, Sevket A, Ozel A, Dansuk R, Kelekci S. The use of HbA1c as an aid in the diagnosis of gestational diabetes mellitus. J Obstet Gynaecol. 2014; 34: 690–2.
24. Christopher D, Saudek M. The Clinical Use of Hemoglobin A1c. J Diabetes Sci Technol. 2009; 3(4): 629–34.
25. Renz PB, Cavagnolli G, Weinert LS, Silveiro SP, Camargo JL. HbA1c Test as a Tool in the Diagnosis of Gestational Diabetes Mellitus. PLoS One, 10(8): e0135989.

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The effect of clomiphene citrate as the first-line treatment of infertile women with polycystic ovarian syndrome (PCOS) in fetal sex: a clinical trial

Infertile with polycystic ovarian

Rasekh Jahromi Athar[1], Mostafadokht Azadeh[1], Raeis Zadeh Jahromi Mojtaba[2], Poorshojai Soolmaz[2], Nasseri Mohamadali[2], Navid Kalani[1]
1Department of Obstetrician and Gynecology, 2Dr. Rasekh Clinic, Jahrom University of Medical Sciences, Jahrom, Iran

Abstract

Aim: The purpose of this study was to determine the effect of clomiphene citrate on fetal sex in PCOS patients who underwent ovulation treatment with clomiphene citrate in comparison with the general population. Material and Method: This study was based on prospective randomized clinical trial comparing the effect of clomiphene as the first-line management of ovulation induction of the PCOS patients and a control group including pregnant ladies without any underlying gynecological disease during January 2013 to December 2015 and was performed in a private infertility clinic (Dr. Rasekh sub special infertility office). The study included 878 patients divided into two groups including 65 patients treating with clomiphene citrate and a control group of 813 pregnant ladies who referred to our office for obstetrics follow-up during this period. Results: Among all the 65 successful pregnancies by infertile women using clomiphene, two pregnancies were as triplets and 16 were twins, and all 85 babies were born alive. Among the 85 babies, 58.82 % were female, and 41.17% were male. After reviewing the drug dosage used by patients, we understood that the majority of mothers with daughters (63%) had used high doses of clomiphene citrate (150-200mg /day) and had repeated cycles of treatment while the initial dosage in this trial was 50-100 mg/day. Discussion: This research shows that the women with anovulatory problems who used clomiphene citrate in a higher therapeutic dosage are more likely to have female babies while using clomiphene citrate in low dosage will not affect the sex of the fetus.

Keywords

Clomiphene Citrate; Infertility; PCOS; Fetal Sex

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Corresponding Author: Azadeh Mostafa Dokht, Department of Obstetrician and Gynecology, Jahrom University of Medical Sciences, Jahrom, Iran.
T: 00981901807 F: 00987154262081 E-Mail: azadeh_mdh@yahoo.com

Introduction

Infertility is a disease of the reproductive system defined as the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse [1]. Ovulatory disorders are common causes of subfertility and infertility due to anovulation or oligo-ovulation caused by Polycystic Ovary Syndrome (PCOS) [2]. PCOS is characterized by ovulatory dysfunction and hyperandrogenism, and it is the most common cause of infertility in women [3]. The diagnosis of PCOS has life-long implications with increased risk of infertility, metabolic syndrome, type 2 diabetes mellitus, and possibly cardiovascular disease [4]. It should be considered in any adolescent girl with hirsutism, persistent acne, menstrual irregularity, or obesity [5]. Approximately two-thirds of patients with PCOS, whether adolescent or adult, have anovulation symptoms [6]. Clomiphene is the most common used pharmacologic agent, and it is considered as the first line treatment for PCOS patients because it's of low cost, relative ease of use and minimal side effects [7]. Clomifene is a mixture of two geometric isomers, enclomifene (E-clomifene) and zuclomifene (Z-clomifene). These two isomers have been found to contribute to the mixed estrogenic and anti-estrogenic properties of clomiphene [8].

Clomifene (INN) or clomiphene (USAN) is a selective androgen receptor modulator (SERM) that increases production of gonadotropins by inhibiting negative feedback on the hypothalamus leading to up-regulation of the hypothalamic–pituitary–gonadal axis [9]. The most common adverse drug reaction associated with the use of clomiphene (>10% of patients) is reversible ovarian enlargement [10].

Less common effects (1-10% of patients) include visual symptoms (blurred vision, double vision, floaters, eye sensitivity to light), headaches, vasomotor flushes (or hot flashes), abnormal uterine bleeding and/or abdominal discomfort [11].

Rare adverse events (<1% of patients) include high blood level of triglycerides, liver inflammation, reversible baldness and/or ovarian hyperstimulation syndrome [12].

Clomifene can lead to multiple ovulation, hence increasing the chance of twins (10% of births instead of ~1% in the general population) and triplets [13].

Some studies have warned that if clomiphene citrate is used for more than a year, it may increase the risk of ovarian cancer [14]. This may only be the case in those who have never been and did not become pregnant. The incidence of fetal and neonatal abnormalities in patients using clomiphene for fertility is similar to that seen in the general population. There is no data to indicate a higher rate of congenital anomalies or spontaneous abortions after using this drug [15].

The purpose of this study was to determine the effect of clomiphene citrate in anovulatory infertile patients with anovulation problems caused by PCOS under ovulation treatment with clomiphene citrate therapy on fetus sex verification in comparison with the general population.

Material and Method

This study is a prospective randomized clinical trial comparing the sexual effect of clomiphene citrate as the first-line management of ovulation induction of the infertile patients and a control group including pregnant ladies without any underlying gynecological disease. This study was performed in a private infertility clinic during 2012 to 2015 and included 878 patients divided into two groups.

The major criteria for the diagnosis of PCOS were oligo- and/or an-ovulation, clinical or biochemical signs of hyperandrogenism, and polycystic ovaries which are in accord with the revised 2003 Rotterdam criteria of PCOS [16], (figure 1). Thyroid function, prolactin level, and husband's sperm analysis were checked for normal values.

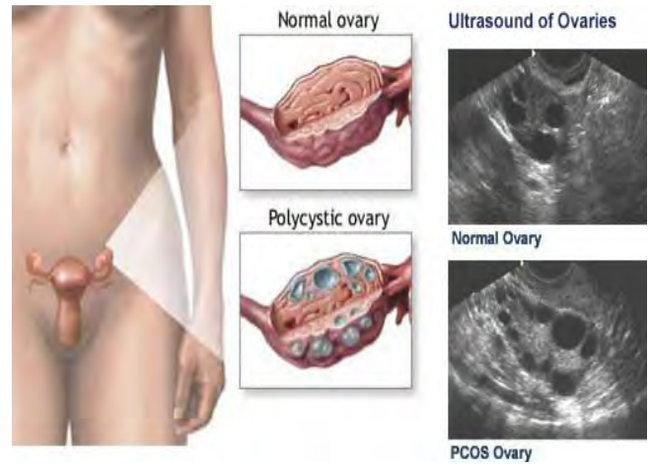

Figure 1. Normal ovary and polycystic ovary

Infertile woman as the definition with diagnoses of PCOS who referred to our sub special infertility clinic and got medication including clomiphene which led to successful pregnancy were included in this study.

Patients with other causes of infertility, infertility which lasts less than one year, and those who got previous treatment(s) for infertility were not included in the study.

The protocol was approved by the ethical investigation committee of our institution, and informed consent was obtained from all the patients after a full informative session. All patients were visited and followed by a single physician.

Based on our statistical data, the fair needed number for performing this study was not equal in each group; All candidates were randomized based on envelope method into either clomiphene citrate group (Group A, n =65) and control group (Group B, n=813).

However, at a dosage of 200 mg, further increments are unlikely to increase pregnancy chances. The patients in the clomiphene group (Group A) received 50-100 mg clomiphene citrate for five days starting from the third day of their menstrual cycle. The standard dosage for first-time takers is 50 or 100 mg of clomiphene per day for five consecutive days, starting early start in the menstrual cycle, usually on the third to fifth day counting from the beginning of the menstrual period. In the absence of success, the dosage can be increased in 4 subsequent cycles with increments of 50 mg (200mg).

To confirm pregnancy β-HCG was measured, and pregnancy was confirmed and followed till nine months to find possible abortion or ectopic pregnancy and finally fetal sex. All data were collected by one physician and by using questionnaire. The data were analyzed by SPSS ver. 22, using Chi-square, Mann-Whitney, and t tests. P values less than 0.05 were considered to be significant.

Results

Among all the 65 successful pregnancies due to using clomiphene citrate by infertile women, 2 pregnancies were as triplets and 16 were twins, and all 85 babies were born alive. Among the 85 babies, 58.82 % were female, and 41.17% were male. After reviewing the drug dosage used by patients, we understood that the majority of mothers with daughters (63%) had used high doses of clomiphene citrate(150-200mg /day) and had repeated cycles of treatment, while the initial dosage in this trial was 50-100 mg/day.

Sex of 813 babies in Group B was as bellow order: [Table 1]

Table 1. Fetal sex in case and control group

Group	MALE	FEMALE	Total
A	50 (58/82%)	35 (41/17%)	85 (100%)
B	417 (51/29%)	396 (48/71%)	813 (100%)

Conclusion

According to the results and in comparison with general population, clomiphene citrate doesn't affect fetal sex in standard dosages (50-100mg/day), but in high doses, it may lead to female sex.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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References

1. Shust Y, Berek JS. Novak's Gynecology. 13th Edition. Philadelphia: Lippincott Williams & Willkins.2002;pp:973-1046.
2. King J. Polycystic ovary syndrome. J Midwifery Womens Health. 2006:51:415–22.
3. Hamilton-Fairley D, Kiddy D, Watson H, Paterson C, Franks. Association of moderate obesity with a poor pregnancy outcome in women with polycystic ovary syndrome treated with low dose gonadotrophin. Br J Obstet Gynaecol. 1992;99(2):128-31.
4. Hull MG. Epidemiology of infertility and polycystic ovarian disease: endocrinological and demographic studies. Gynecol Endocrinol. 1987;1(3):235-45.
5. Nadir R, Farid D. Evanthia Diamanti-Kandarakis. Diagnosis and Management of Polycystic Ovary Syndrome. Springer. 2006; p. 243. ISBN 978-0-387-09717-6
6. Speroff L, Glass RH, Kase NG. Clinical gynecologic endocrinology and infertility. 6th Edition. Philadelphia: Lippincott. 2005;pp:1014-58.
7. Gardner DK, Howles CM, Weissmann A. Textbook of Assisted Reproductive Techniques. 2nd Edition. Florencel, Toms. 2002;p:429-539.
8. Badawy A, Elnashar A, Totongy M. Clomiphene citrate or aromatase inhibitors for superovulation in women with unexplained infertility undergoing intrauterine insemination: A prospective randomized trial. Fertil Steril. 2009;92:1355–9.
9. Biljan MM, Hemmings R, Brassard N. The Outcome of 150 Babies Following the Treatment With Letrozole or Letrozole and Gonadotropins. 2005 doi:10.1016/j.fertnstert .07.230
10. Tulandi T, Martin J, Al-Fadhli R. Congenital malformations among 911 newborns conceived after infertility treatment with letrozole or clomiphene citrate. Fertility and Sterility 2006;85 (6): 1761–5. doi:10.1016/j.fertnster .03.014.
11. Lee VCY, Yu EH, Yeung WSB, Ho PCH . Misoprostol With or Without Letrozole Pretreatment for Termination of Pregnancy. OB Gyn. 2006;117(2):317–23). doi:10.1097/AOG.0b013e3182073fbf.
12. Scott RT, Leonardi MR, Hofmann GE, Illions E. A prospective evaluation of clomiphen citrate challenge test, screening in general infertile population. Obstet Gunecol. 1993:82: 539- 45.
13. Navot D, Rosenwak SZ,Margalioth EJ. Prognostic of female fecundity. Lancet. 1987;11: 645-7.
14. Morret C, Toscano V. Dynamic evaluation of ovarian reverse and abnormal androgen excess in women. Endocrinol invest. 2003:27(7):114-23
15. Simpson ER. Sources of estrogen and their importance. The Journal of Steroid Biochemistry and Molecular Biology. 2003;86(3–5):225–30. doi:10.1016/S0960-0760(03)00360-1.
16. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril. 2004;81(1):19–25.doi:10.1016/j.fertnstert.2003.10.004.

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Factors affecting treatment outcome of acute promyelocytic leukemia in Egyptian patients

Hamdy M. Zawam[1], Mohsen M. Mokhtar[1], Rasha Salama[1], Samy A. Alsirafy[2], Mai K. Bishr[1,3]
[1]Kasr Al-Ainy Center of Clinical Oncology & Nuclear Medicine (NEMROCK), Cairo University, Cairo, Egypt,
[2]Palliative Medicine Unit, Kasr Al-Ainy Center of Clinical Oncology & Nuclear Medicine (NEMROCK), Cairo University, Cairo, Egypt,
[3]Department of Radiotherapy, Children's Cancer Hospital Egypt (CCHE), Cairo, Egypt

Abstract

Aim: Acute promyelocytic leukemia (APL) is a peculiar subtype of acute myeloid leukemia clinically and morphologically. To date, only a few studies reported the treatment outcome of APL in developing countries. Thus, we investigated the challenges and factors affecting APL treatment in Egypt. Material and Method: This study included 27 APL patients treated at Kasr Al Ainy Center of Clinical Oncology and Nuclear Medicine (NEMROCK) – Cairo University hospital, Egypt from 2010 till 2014. Results: The mean age at presentation was 35 years, and intermediate and high-risk Sanz scores constituted 44% and 30% of patients, respectively. Complete remission (CR) was achieved by 17 patients (63%), 1 patient had a refractory disease (3.7%), and the response could not be evaluated in 5 patients. No deaths were encountered before treatment, and early mortality rate was 14.8% (n=4). All patients in CR received consolidation therapy, and molecular remission was achieved by 14 patients (82.4%). By December 2015, relapse occurred in 5 patients (29.4%). The median disease-free survival (DFS) was 27.1 months, the mean overall survival (OS) was 84.4 months, and the median OS was not reached. Factors affecting survival included: body mass index (DFS: p-0.012, OS: p-0.009), type of induction regimen (OS: p-0.007), treatment interruption (OS: p-0.035), number of consolidation cycles (OS: p-0.001), duration of maintenance therapy (DFS: p-0.018) and response to salvage therapy (OS: p-0.046). Discussion: Our findings elucidate the challenges met by developing countries owing to limited resources and financial constraints.

Keywords

Acute Myeloid Leukemia (AML); Acute Promyelocytic Leukemia (APL); Survival; Mortality Rate; Relapse.

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Corresponding Author: Mai K. Bishr, Department of Radiotherapy, Children's Cancer Hospital Egypt (CCHE), 1 Seket Al-Emam Street, El-Madbah El-Kadeem Yard, El-Saida Zenab, Cairo, Egypt. GSM: +201224003091 F.: +202-25351745 E-Mail: mai.khaled@57357.org, mai.khaled.bishr@hotmail.com
Orcid ID: 0000-0002-9124-7492

Introduction

Acute myeloid leukemia (AML) is one of the challenging hematological malignancies worldwide. In adults, it is the commonest type of leukemia with the highest 5-year relative survival reported in acute promyelocytic leukemia (APL) patients compared to all other subtypes [1]. The outcome of APL patients has improved over the years and patients who achieved complete remission (CR) for at least 3 years have a very low incidence of late relapses [2]. Several clinical situations represent a daunting challenge in the management of AML patients, posing a high risk of increased morbidity and mortality. In APL patients, hemorrhagic complications remain the most frequent cause of mortality. Thus, prompt diagnosis and recognition of any coagulation defect is imperative at presentation [3].

This retrospective study sheds light on challenges and treatment outcome of APL patients at a single cancer center in Egypt, during the period from January 2010 to December 2014.

Material and Method

The current study was designed to evaluate treatment outcome of APL patients treated at Kasr Al Ainy Center of Clinical Oncology and Nuclear Medicine (NEMROCK) – Cairo University Hospital, Egypt. During the period from January 2010 to December 2014, 27 APL cases were treated at our center, and they represent our study cohort. The study was approved by the ethical committee and institutional review board.

Patients' medical records were reviewed for baseline clinical characteristics at presentation. Patients diagnosed with APL were identified by the presence of t(15;17), and risk stratified according to Sanz score [4]. All-trans-retinoic-acid (ATRA) was initiated immediately at presentation based on clinical and/or morphological suspicion. A dose of 45mg/m^2 in 2 divided doses was received till morphological remission or for a maximum of 30 days. When the diagnosis of APL was confirmed, anthracyclines were added to ATRA for 3 days: idarubicin 12 mg/m^2/day, doxorubicin 25mg/m^2/day or mitoxantrone 10mg/m^2/day in case of unavailability of idarubicin. Cytarabine was added in the context of "7+3 protocol" in 5 patients, while ATRA single agent was reserved for old patients with a poor general condition.

After complete recovery of blood counts and clearance of blast cells, bone marrow examination was done for response assessment. Patients who were refractory to treatment received a second induction course using the same or alternative anthracycline, with cytarabine 100 mg/m^2/day continuous infusion for 7 days in initially high-risk patients. Patients in remission received 1-3 consolidation cycles of ATRA 45 mg/m^2 for 15 days in combination with an anthracycline for 3 days. Molecular status was assessed using reverse transcriptase polymerase chain reaction (RT-PCR) for PML-RARA transcripts. Patients who achieved complete molecular remission (CR) were scheduled for risk-adapted maintenance therapy. Low-risk patients were not offered maintenance treatment, intermediate risk patients were offered maintenance for 6 months, while high-risk patients were offered treatment for 2 years. Maintenance therapy consisted of 6-mercaptopurine 60mg/m^2/day, oral methotrexate 20mg/m^2 weekly and ATRA 45mg/m^2 for 15 days every 3 months.

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 14 (SPSS Inc., Chicago, IL) for Windows. Data was presented as numbers and percentages or mean ± standard deviation. OS was calculated from the date of the first presentation to the date of death. DFS was calculated from the date of bone marrow-documented CR to the date of relapse. The Kaplan-Meier method was used for survival analysis, and the significance of the difference in survival was determined using the log-rank test.

Results

Patients' characteristics

Twenty-seven patients diagnosed as APL were identified in our study, and their baseline characteristics are shown in table 1. A slight female predominance was noted (male: female 1:1.25), and the majority of patients (74.1%) aged between 20 and 60 years. More than half of patients presented with ECOG performance status 1 and bleeding tendency was the most common presenting symptom. All patients suffered from anemia and thrombocytopenia, while only 1 patient presented with hyperleukocytosis (defined as TLC >100X10^3/mL). Intermediate and high-risk Sanz scores constituted 44% and 30% of our patients' cohort, respectively.

Table 1. Baseline characteristics of 27 APL patients.

Variable	Number	Percentage
Gender		
Male	12	44.4%
Female	15	55.6%
Age		
Range	17-67	
Mean	35	
<20 years	3	11.1%
20-60 years	20	74.1%
>60 years	4	14.8%
Performance status (ECOG)		
1	15	55.6%
2	7	25.8%
3	5	18.6%
Body mass index		
Range	15.1-38.6	
Mean	26	
Underweight (<18.5)	2	7.4%
Normal (18.5 - ≤25)	7	25.8%
Overweight (>25 – 30)	2	7.4%
Obese (>30)	6	22.2%
Unknown	10	37.2%
Clinical manifestations		
Anemic symptoms	17	63%
Bleeding tendency	23	85%
Recurrent infections	12	44.4%
Hemoglobin level (g/dL)		
Range	3.7-9	
Mean	6.5	
Total leukocyte count (/mL)		
Range	0.6-358 X10^3	
Mean	33 X10^3	
Platelet count (/mL)		
Range	7-59 X10^3	
Mean	24.4 X10^3	
Sanz score		
Low risk	2	7%
Intermediate risk	12	44%
High risk	8	30%
Unknown	5	19%

APL: acute promyelocytic leukemia; ECOG: the Eastern Cooperative Oncology Group

Treatment results

All 27 APL patients started receiving ATRA upon their presentation, based on clinical and/or laboratory suspicion. The majority of patients (63%) received either doxorubicin or mitoxantrone in combination with ATRA, while 14.8% of patients received single-agent ATRA (table 2). Only 3 patients (11.1%) necessitated treatment interruption due to development of either differentiation syndrome or febrile neutropenia. First complete remission (CR1) was achieved by 15 patients (55.6%), 3 patients (11.1%) were refractory to treatment, while treatment-related mortality was encountered in 4 cases (14.8%). The response was inevaluable in 5 patients due to loss of follow up.

The refractory cases were scheduled for a second induction cycle in addition to ATRA. Two patients received 7+3 protocol and achieved CR, while one patient had persistent refractory disease after receiving doxorubicin. Overall, CR was achieved by 17 patients (63%), and 1 patient had persistent refractory disease (3.7%). No deaths were encountered before starting treatment, and 4 patients died within 30 days from induction therapy (14.8%).

All patients in CR received 1-3 consolidation cycles. Fourteen patients (82.4%) achieved molecular remission and received maintenance treatment, while 3 patients lost to follow up and didn't receive any further treatment. By December 2015, relapse occurred in 5 patients (29.4%), while 12 patients (70.6%) were still alive in remission. Out of 5 relapsed patients, 1 patient died of intracranial hemorrhage before starting active treatment. Salvage therapy was given in 4 patients; 3 of them achieved the second remission, and 1 died of uncontrolled infection.

Table 2. Results of first induction therapy in 27 APL patients.

Variable	Number	Percentage
Induction regimen (+ATRA)		
7+3 protocol	5	18.5%
Doxorubicin	9	33.3%
Idarubicin	1	3.7%
Mitoxantrone	8	29.7%
ATRA single agent	4	14.8%
Treatment interruption		
Yes	3	11.1%
No	24	88.9%
Response		
CR1	15	55.6%
Refractory	3	11.1%
Death	4	14.8%
Unknown	5	18.5%

APL: acute promyelocytic leukemia; ATRA: all-trans-retinoid acid; CR1: first complete remission.

Survival and mortality outcomes

Of our cohort of 27 APL patients, 17 patients achieved complete remission, and their median disease-free survival (DFS) was 27.1 months. The mean overall survival (OS) of our 27 APL cases was 84.4 months (95% CI: 51.4 – 117.4), and the median OS was not reached. Several factors were proven to significantly affect survival in our patients, including body mass index (BMI), type of first induction regimen, its interruption, number of consolidation cycles received, duration of maintenance therapy and response to salvage therapy. On the other hand, age, gender, performance status, and hyperleukocytosis lacked significant impact on survival outcomes.

BMI has been shown to influence both disease-free and overall survival significantly. Normal BMI patients had the highest survival outcomes while underweight patients had the lowest outcomes when compared to other BMI groups (p-value 0.009) (figure 1 and 2). Patients who received single-agent ATRA as first induction had a poor median OS of 5.6 months when compared to those who received ATRA in combination with chemotherapy (median OS was not reached) (p-value 0.007) (figure 3). Moreover, interruption of induction therapy significantly altered the survival of our patients, as illustrated in figure 4. Patients who necessitated treatment interruption had a lower median OS of 9.2 months, as opposed to those who completed their full course of treatment (median OS was not reached) (p-value 0.035).

As regards post-remission treatment, patients who received only 1 consolidation cycle had the lowest overall survival outcome (p 0.001) when compared to those who completed 3 cycles. On the other hand, patients who received ≥ 12 months of maintenance therapy had significantly longer DFS than those received < 12 months (figure 5). Also, patients who were refractory to salvage therapy had an OS of 23.8 months, as opposed to patients who achieved CR2 (median OS was not reached) (p-value 0.046).

A total of 7 patients (26%) died by December 2015 in our study. Treatment-related deaths accounted for 71% of all deaths; 57% of deaths occurred during induction treatment (4 patients: 1 died of intracranial hemorrhage, and 3 died of febrile neu-

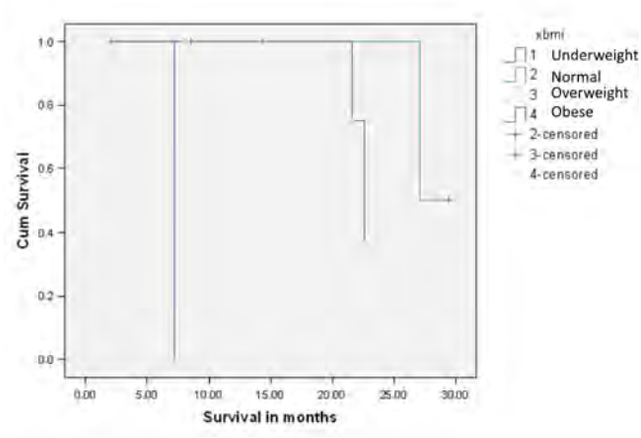

Figure 1. Impact of BMI on DFS of 17 APL patients in remission.

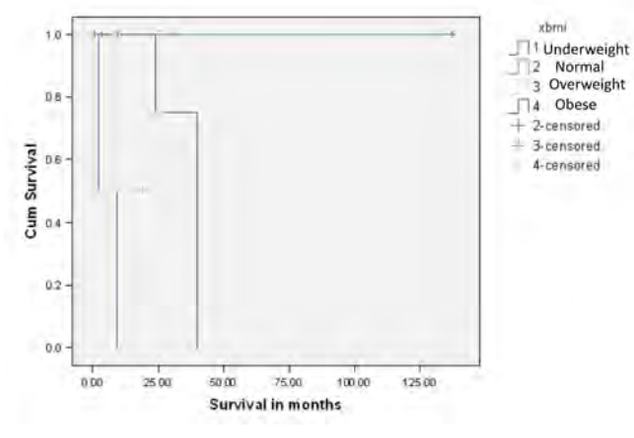

Figure 2. Impact of BMI on overall survival in 27 APL patients.

tropenia), while 14% occurred during salvage therapy. On the other hand, disease-related mortality accounted for 29% of deaths due to either relapse or refractory disease.

Discussion

APL is a peculiar subtype of AML that usually presents with abrupt onset, with a high early mortality rate because of hemorrhage and coagulopathy. Once the diagnosis is suspected, it should be managed as a medical emergency, and treatment must be started immediately with ATRA therapy **[5].** A risk-adapted strategy was designed by the cooperative group Programa Español de Tratamientos en Hematología (PETHEMA) based on the combination of ATRA and anthracyclines (PETHEMA LPA99 and LPA2005 trials) and demonstrated high anti-leukemic efficacy in APL patients **[6].**

This study included 27 APL patients, constituting 23% of AML patients treated at our center during the period 2010-2014. A close proportion of APL among AML diagnoses has been reported in Mexico (20%). Whereas a higher proportion has been documented in Brazil (28%), and Latin America (37.5%) **[7].** Ages of our patients ranged from 17 to 67 years, with a mean of 35 years. A male: female ratio of 1:1.25 was demonstrated showing a slight female predominance. The bleeding tendency was the most frequent clinical manifestation at presentation (85% of cases), and the majority of our patients were of intermediate risk Sanz score (44%), while 30% were high risk. Comparable epidemiological features of Egyptian patients were demonstrated in a retrospective study held at National Cancer Institute, Cairo. The median age was 29 years (range: 3-72), and there was a slight male predominance (53%). Bleeding was the presenting symptom in 79% of cases, whereas intermediate and high-risk Sanz scores constituted 49% and 34% of patients, respectively **[8].**

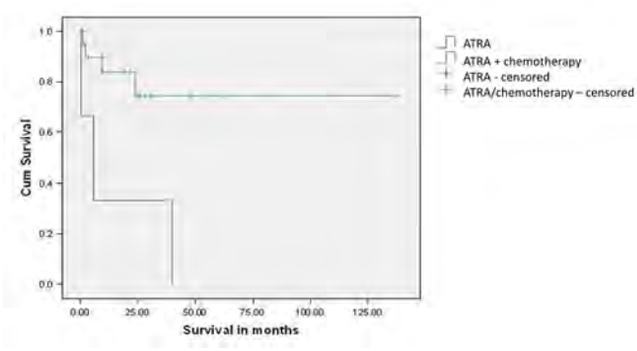

Figure 3. Overall survival of 27 APL patients according to type of 1st induction regimen.

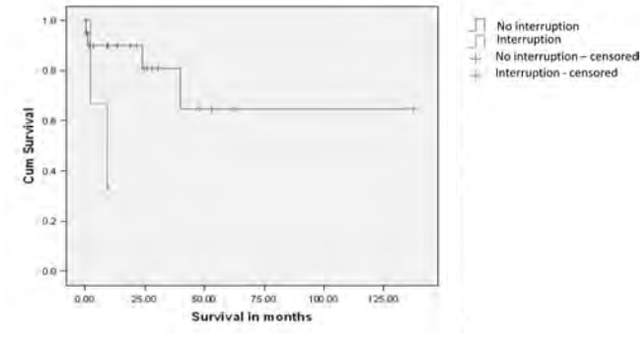

Figure 4. Impact of induction treatment interruption on overall survival of 27 APL patients.

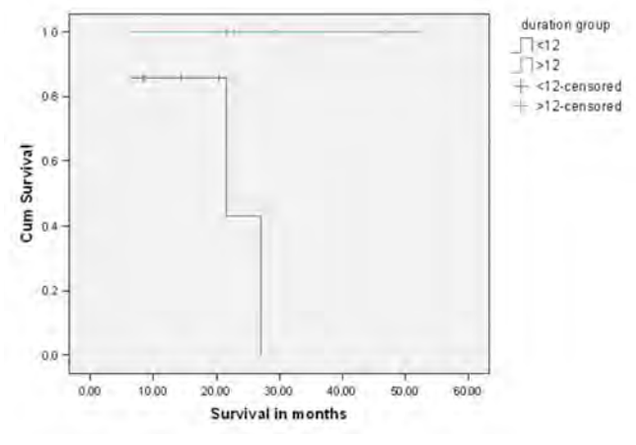

Figure 5. DFS of 14 APL patients who received maintenance therapy according to its duration.

When BMI was used for patient stratification, normal BMI was the most common group followed by obesity (25.8% and 22.2%, respectively). Our study revealed a strong correlation between BMI and both DFS and OS, as normal BMI patients had the highest survival outcomes compared to other BMI groups (DFS p=0.012, OS p=0.009). This finding is in concordance with a study conducted on 446 APL patients to investigate the role of obesity as an adverse prognostic factor. It was shown that obese APL patients had significantly shorter OS and DFS than non-obese patients **[9].**

Several treatment variables were proven to affect the survival of our patients adversely. Although the use of ATRA single agent was restricted to 4 elderly patients with debilitating co-morbidities, it was associated with a significant reduction of OS (5.6 months vs. OS not reached in combination regimen) (p=0.007). However, the small number of cases receiving ATRA cannot reliably account for significance. The poor outcome could also be partly attributed to the old age and poor performance status of those patients.

During induction therapy, adverse events frequently impose considerable clinical challenges that necessitate treatment interruption. In this study, 2 patients developed differentiation syndrome and 1 patient suffered from severe febrile neutropenia during induction therapy. The interruption of treatment significantly hampered OS in those patients when compared to those who completed their treatment course (9.2 months vs. OS not reached, respectively) (p=0.035). This observation emphasizes the importance of timely delivery of treatment and optimal supportive care in APL patients.

After two induction cycles, the overall CR rate in our study was 63% which is markedly lower than that reported in PETHEMA LPA99 and APL2000 trials (92.9% and 97.2%, respectively). Moreover, our early mortality rate was higher than that reported in those trials (14.8% vs. 6.8% in PETHEMA LPA99 vs. 2.8% in APL2000 trials) **[10].** However, it is noteworthy that mortality rates from several institute-based or population-based studies have been shown to be considerably higher than in clinical trials. The highly selected patients within a clinical trial setting do not reflect the population characteristics accurately. In addition, clinical trials do not fully account for patients who die early of hemorrhagic complications. This is why population studies are more likely to represent the real-world incidence of early mortality rates **[11].**

Several studies concluded that early mortality rates in APL patients remain to be a daunting challenge, particularly in developing countries. An earlier study in Egyptian patients reported lower induction mortality (4.8% vs. 14.8% in our study); however, another 7.5% of patients died early before treatment, which was not encountered in our study **[8].** Another study in the United Arab Emirates revealed an early mortality rate of 11.9%, a slightly lower figure than that reported in our patients **[12].** Early APL deaths seem to be a distressing problem in some developed countries as well. A Canadian population-based study and a SEER analysis of patients treated in the United States reported higher early mortality rates than that observed in our institute (21.8% vs. 17.3% vs. 14.8%, respectively) **[11, 13].**

Other treatment variables that were shown to affect survival in our patients include the number of consolidation cycles and duration of maintenance treatment. All patients in remission received 1-3 consolidation cycles, where patients who completed 3 cycles exhibited the longest OS (p=0.001). All patients in molecular remission following consolidation treatment proceeded to receive maintenance therapy, the duration of which impacted DFS. Half of our patients received maintenance for less than 12 months, which resulted in a significantly shorter DFS than those who received treatment for ≥12 months (p=0.018). However, no difference was noted in OS. Of note, all patients who received maintenance treatment for less than 12 months were of the intermediate risk group, except for 1 high-risk patient who was still on maintenance therapy by the end of the study.

In contrast with our results, the AIDA 0493 trial demonstrated that maintenance treatment did not provide any survival advantages for patients achieving molecular remission. Bearing in mind that the relative benefit of maintenance therapy depends on prior induction and consolidation treatment, the intensive regimens used in that trial might have abolished the possible benefit of maintenance treatment **[14].** On the other hand, a meta-analysis of 10 randomized trials including 2,072 APL patients concluded that any maintenance treatment compared with observation prolongs DFS but not OS **[15].**

Out of 17 patients in remission in our study, 5 patients (29.4%) eventually relapsed. Two of them had lost follow up after consolidation cycles and did not receive maintenance treatment, and the remaining three patients had received maintenance for less than 12 months. One of the relapsed patients died of intracranial hemorrhage before commencing salvage therapy, while the remaining 4 patients received ATRA in combination with either adriamycin in 3 patients, or "7+3 protocol" in 1 patient. A second complete remission was achieved in 3 cases (75%) and 1 patient (25%) died of uncontrolled infection. Both PETHEMA LPA99 and APL2000 trials reported lower relapse incidence and higher deaths in remission than that experienced by our patients. The cumulative incidence of relapse at 3 years was 7.4% and 12% respectively, while 29.4% of our patients eventually relapsed within 3 years. Death in remission occurred in 1.3% and 2.9% of patients in both trials respectively, whereas none of our patients died in remission **[10].**

In conclusion, we realize the several limitations of a retrospective study design and a small number of patients. However, it is obvious that treatment outcome of APL in Egyptian patients is in dire need of improvement. The inconsistent supply of chemotherapeutics and supportive care facilities, as well as financial constraints, are some of the greatest challenges faced by healthcare policies in a developing country like Egypt.

Ethical Responsibilities

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of interest

All authors declare there are no conflict of interests.

Source of fund

None.

References

1. Dores GM, Devesa SS, Curtis RE, Linet MS, Morton LM. Acute leukemia incidence and patient survival among children and adults in the United States, 2001-2007. Blood. 2012; 119(1): 34-43. Doi: 10.1182/blood-2011-04-347872.
2. Wang ZY, Chen Z. Acute promyelocytic leukemia: from highly fatal to highly curable. Blood. 2008; 111(5): 2505-15. Doi: 10.1182/blood-2007-07-102798.
3. Breen KA, Grimwade D, Hunt BJ. The pathogenesis and management of the coagulopathy of acute promyelocytic leukaemia. British journal of haematology. 2012; 156(1): 24-36. Doi: 10.1111/j.1365-2141.2011.08922.x.
4. Sanz MA, Montesinos P, Vellenga E, Rayón C, de la Serna J, Parody R, et al. Risk-adapted treatment of acute promyelocytic leukemia with all-trans retinoic acid and anthracycline monochemotherapy: long-term outcome of the LPA 99 multicenter study by the PETHEMA Group. Blood. 2008; 112(8): 3130-4. Doi: 10.1182/blood-2008-05-159632.
5. Yoo ES. Recent advances in the diagnosis and management of childhood acute promyelocytic leukemia. Korean journal of pediatrics. 2011; 54(3): 95-105. Doi: 10.3345/kjp.2011.54.3.95.
6. Sanz MA, Montesinos P, Rayón C, Holowiecka A, De La Serna J, Milone G, et al. Risk-adapted treatment of acute promyelocytic leukemia based on all-trans retinoic acid and anthracycline with addition of cytarabine in consolidation therapy for high-risk patients: further improvements in treatment outcome. Blood. 2010; 115(25): 5137–46. Doi: 10.1182/blood-2010-01-266007.
7. Testi AM, D'Angiò M, Locatelli F, Pession A, Coco FL. Acute promyelocytic leukemia (APL): Comparison between children and adults. Mediterranean journal of hematology and infectious diseases. 2014; 6(1): e2014032. Doi: 10.4084/MJHID.2014.032.
8. Khorshid O, Diaa A, El Moaty MA, El Fatah RA, El Dessouki I, El Hamid MA, et al. Clinical features and treatment outcome of acute promyelocytic leukemia patients treated at cairo national cancer institute in Egypt. Mediterranean journal of hematology and infectious diseases. 2011; 3(1): e2011060. Doi: 10.4084/MJHID.2011.060.
9. Castillo JJ, Mulkey F, Geyer S, Kolitz JE, Blum W, Powell BL, et al. Relationship between obesity and clinical outcome in adults with acute myeloid leukemia: A pooled analysis from four CALGB (alliance) clinical trials. American journal of hematology. 2016; 91(2): 199-204. Doi: 10.1002/ajh.24230.
10. Ades L, Sanz MA, Chevret S, Montesinos P, Chevallier P, Raffoux E, et al. Treatment of newly diagnosed acute promyelocytic leukemia (APL): a comparison of French-Belgian-Swiss and PETHEMA results. Blood. 2008; 111(3): 1078-84. Doi: 10.1182/blood-2007-07-099978.
11. Park JH, Qiao B, Panageas KS, Schymura MJ, Jurcic JG, Rosenblat TL, et al. Early death rate in acute promyelocytic leukemia remains high despite all-trans retinoic acid. Blood. 2011; 118(5): 1248-54. Doi: 10.1182/blood-2011-04-346437.
12. Hassan IB, Al Zaabi MR, Alam A, Hashim MJ, Tallman MS, Kristensen J. Characteristics features and factors influencing early death in Acute promyelocytic leukemia; Experience from United Arab Emirates (UAE). International Journal of Hematology. 2017; 106(1): 90-8. Doi: 10.1007/s12185-017-2211-7.
13. Paulson K, Serebrin A, Lambert P, Bergeron J, Everett J, Kew A, et al. Acute promyelocytic leukaemia is characterized by stable incidence and improved survival that is restricted to patients managed in leukaemia referral centres: a pan-Canadian epidemiological study. British journal of haematology. 2014; 166(5): 660-6. Doi: 10.1111/bjh.12931.
14. Avvisati G, Lo-Coco F, Paoloni FP, Petti MC, Diverio D, Vignetti M, et al. AIDA 0493 protocol for newly diagnosed acute promyelocytic leukemia: very long-term results and role of maintenance. Blood. 2011; 117(18): 4716-25. Doi: 10.1182/blood-2010-08-302950.
15. Muchtar E, Vidal L, Ram R, Gafter-Gvili A, Shpilberg O, Raanani P. The role of maintenance therapy in acute promyelocytic leukemia in the first complete remission. Cochrane Database Syst Rev. 2013; 3: CD009594. Doi: 10.1111/ajco.12003.

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Effect of virtual reality method and multimedia system on burn patients' pain during dressing

Hossein Ebrahimi[1], Hossein Namdar[1], Mohammad Ghahramanpour[1], Mansour Ghafourifard[2], Saeed Musavi[3]
[1]Department of Psychiatric Nursing, Faculty of Nursing and Midwifery, Tabriz University of Medical Sciences,
[2]Department of Medical Surgical Nursing, Faculty of Nursing and Midwifery, Tabriz University of Medical Sciences,
[3]Department of Biostatistics, Faculty of Health and Nutrition, Tabriz University of Medical Sciences, Tabriz, Iran

Abstract

Aim: Pain is the most important factor which forces burn patients to look for the health system's help. One of the non-pharmacological methods of pain relief for burn patients is virtual reality, which is a challenging technique because virtual reality headset itself may cause claustrophobia and anxiety followed by the cycle of anxiety and pain via creating a closed space. The present study is aimed to determine the effect of both methods of virtual reality and multimedia system on the burn patients' pain during dressing. Material and Method: The present clinical trial was conducted on 60 burn patients hospitalized in Sina Hospital, Tabriz, in accordance with the inclusion criteria using the technique of random allocation to three groups of virtual reality, multimedia system, and control. The sounds and virtual images were played through headsets in the virtual reality group and an LCD in the multimedia system group during dressing and dressing changes in five consecutive days. Data analysis was performed using a demographic questionnaire as well as the linear-visual scale of pain intensity. Furthermore, the repeated measurement test was used to investigate the changes in pain over time and compare the control group with the multimedia system and virtual reality groups. Results: Comparing the three groups indicated a significant difference (p=0.006). The results showed no significant difference between the virtual reality and control groups (p>0.05), but the pain score in the multimedia group was significantly different from the control group on the first (p= 0/02), second (p =0.008), third (p= 0/02) fourth (p =00) and fifth (p=0.03) days of the intervention. Comparison of multimedia and virtual reality showed the pain score in the virtual reality was higher than multimedia on the fourth day (p =0/002) of intervention. Discussion: Multimedia system can have positive effects on reduction of the burn patients' pain compared to virtual reality; therefore, it is recommended to use this method for controlling the burn patients' pain.

Keywords

Virtual Reality; Multimedia System; Pain; Burn

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Corresponding Author: Mohammad Ghahramanpour, Department of Psychiatric Nursing, Faculty of Nursing and Midwifery, Tabriz University of Medical Sciences, Tabriz, Iran. T.: +9833772513, +9832314763 E-Mail: amghahramanpur@gmail.com

Introduction

Burn is considered as one of the worst traumatic injuries resulting in a life threat all around the world (1). Annually, 500000 cases of burning occur in the United States, nearly 40000 of which are severe and require hospitalization, and about 3400 deaths occur due to burns (2). In Iran, a large number of burns occur annually so that, each year, more than 100000 cases of burns are reported in specialized burn centers, nearly 8000 to 9000 cases of which lead to hospitalization (3).

Burn injury is a physically and mentally very painful experience since patients experience severe pains during their treatment, especially during dressing changes (4), which significantly affects their mental health (5). Thus, the health care providers are faced with the challenge that how to help the burn patients adapt to the distressing and painful care procedures and interventions during the acute phase (6). The poor control of pain is associated with physiological and psychological results, including intractable pain, depression, and post-traumatic stress, and also extensively with suicidal thoughts (7).

Further, appropriate control of pain, resulted from therapeutic actions, would lead to a reliable relationship between the burn patients and the treatment staff, a reduction in mental disorders such as depression and post-traumatic stress, as well as progress in the patient's admission and cooperation in the recovery process (8). One of the basic methods for pain control among the burn patients is the use of opioids (narcotic drugs), which is associated with many side effects (9); on the other hand, the non-pharmacological pain control methods, besides having fewer side effects, are both non-addictive and non-invasive (10). One of the non-pharmacological and highly effective methods for reducing pain perception is distraction (11). When the pain drug treatments are insufficient and drugs are associated with side effects, the non-pharmacological treatments, such as distraction, would be effective in pain control (12). Furthermore, the non-pharmacological methods of pain control are easy and inexpensive with minimum side effects (13). One of the distraction methods for reducing the pain perception, which is based on the behavioral interventions, is the virtual reality, which is noticeable among the burn patients in cases that the analgesia are not created sufficiently. According to the reports, images and sounds of the virtual reality have lowered the patients' feeling of pain (14). The interventions in virtual reality are based on the patient's distraction from acute pain (15). Several studies have shown that virtual reality leads to the reduced pain during the painful procedures (16). A clinical trial was conducted by Faber et al. (2013) in order to determine the effect of frequent use of virtual reality on pain during the dressing change among adults and infant burn patients in the United States. The obtained results showed that the frequent use of this technique would significantly reduce the burn patients' pain (6). Another clinical trial was conducted by Schmitt et al. (2011) in order to determine the effect of virtual reality during physical therapy on the infant burn patients' pain, the results of which showed that the virtual reality would significantly reduce the pain (17). Hoffman et al. (2012), in a study on the effect of virtual reality on the infant burn patients' pain during occupational therapy, demonstrated that the virtual reality would lead to a significant reduction in the infants' burn pains during the occupational therapy (18). There is a two-way relationship between the burn patients' pain and mental problems, such as anxiety, which means that severe pain leads to the increased anxiety and, subsequently, increased intensity of pain among burn patients during therapeutic and care activities (19, 20). Studies have represented that a closed space would result in the claustrophobia and anxiety (21); therefore, by creating a closed space, the virtual reality headset might cause claustrophobia and anxiety in the patient and affect results of the study. Moreover, some studies have demonstrated applications of the multimedia system in various areas of burns for reducing the pain (25, 26, 27). However, none of these studies have directly compared the effects of these two methods on pain relief. In order to investigate the effect of claustrophobia and anxiety using virtual reality headset and creating the cycle of anxiety and pain, the present study was conducted to determine the effects of the two virtual reality and multimedia system methods on the burn patients' pain during dressing. In the virtual reality group, the images and sounds of a waterfall were played using the virtual reality headset, while in the multimedia system group, the same images and sounds were played in an open and quiet environment using an LCD; then, results of both interventions were compared. Thus, the evidence provided for health care providers, including nurses, can be more effective in choosing the virtual reality and multimedia system distraction as an appropriate method of pain control.

Material and Method

The present study was a randomized clinical trial conducted to compare the effects of virtual reality and multimedia system methods on burn patients' pain during dressing in the Burns Ward of Sina Hospital, Tabriz University of Medical Sciences, Iran. In this study, the samples were selected based on the inclusion criteria using convenient sampling method; then, after obtaining the informed consent, all the 60 burn patients were randomly allocated to the three groups (virtual reality, multimedia system, and control), each of which included 20 subjects. The inclusion criteria included hospitalization since the entry into the Burns Ward, no history of burns, age of above 18 for male and female patients, tendency to participate in the study, being conscious and oriented, no drug addiction, general health over the past month, no eyesight and hearing problem, below 25% and second-degree burns, being in acute phase (42 to 72 hours), no numbness in target organs, and no diabetes. On the other hand, the exclusion criteria included the lack of tendency to continue cooperation, transmission to any section other than the Burns Ward, absence in more than one session, receiving sedatives without prescription, and receiving skin graft.

Data collection was performed using a demographic characteristics questionnaire (including age, gender, education level, sedatives intake, and burn percentage).The dressing pain intensity was examined by VAS (Visual Analog Scale), which was a 10-cm and 11-number line with a certain range so that the numbers 0 and 10 indicated no pain and intolerable pain, respectively. The subjects were asked to mark a point on the line corresponding to the intensity of their pain or express its numeric value to the researchers. These tools are widely used and their validity and reliability in acute pains have been proved (22). Moreover,

reliability of this tool has been confirmed by Mazloum using retest method so that this scale was completed by the researcher for 10 individuals in two steps and, then, its reliability was announced to be equal to 92% (23).

After covering the administrative procedures, obtaining the required administrative licenses, and registering the clinical trial in the Iranian Registry of Clinical Trials (IRCT), the researcher initiated sampling by referring to the Burns Ward in Sina Hospital, Tabriz. Once the subjects were allocated to the three groups (control, virtual reality, and multimedia system), similar virtual images (images and waterfall sounds) were played by the researcher. In the virtual reality group, the images and sounds were played through a virtual reality-specific headset, while in the multimedia system, the images and sounds were played through an LCD. The procedures were such that this technique was performed one session a day during the process of dressing on 5 consecutive days from the third day to the seventh day of burns (according to Faber and Schmitt) on the morning shift in order to prevent interference with other tasks of the relevant ward. After collecting and coding the data and importing them into SPSS V.18 software, data analysis was performed using the data analysis tests. To evaluate the changes in pain over the time and also compare the control group with the multimedia system and virtual reality groups, the repeated measurement analysis was used, and also the pre-intervention measurements were included in the model as the covariate.

Results

The demographic characteristics included age, gender, education, burn percentage, and sedative intake. Table (1) represents comparison of the three groups in terms of statistical differences. According to Chi-square test results, none of the three groups had difference in terms of demographic characteristics including gender, education, sedatives intake. Furthermore, ANOVA indicated no significant difference between the three groups in terms of age distribution and burn percentage.

The repeated measurement test results showed a significant difference between the three groups (p=0.006) (Table-2).

The pre-intervention measurements were included in the repeated measurement analysis model as covariate. The results of repeated measurement analysis showed no significant difference between the virtual reality and control groups (p>0.05), but the pain score of the multimedia group was significantly different from the control group on the first (p =0.02), second (p =0.008), third (p= 0/02), fourth (p =0.00), and fifth (p =0.03) days of the intervention. Comparison of multimedia and virtual reality showed the pain score of the virtual reality group was higher than multimedia group on the fourth day (p=0.002) of intervention. Table (3) shows the repeated measurements in accordance with the intervention days and Figure (1) shows the pain observation procedure on consecutive days.

Discussion

Results of the present study demonstrated that both virtual reality and multimedia system methods reduced the burn dressing pain, except that the virtual reality resulted in the relative control of the burn dressing pair, while the multimedia system led to a significant reduction in the burn dressing pain. No statistical difference was obtained in terms of the demographic and clinical variables such as age, gender education level, burn percentage, and sedatives intake; therefore, the obtained results indicating effectiveness of the type of the method on level of the burn dressing pain among burn patients were highly reliable and not influenced by the confounding factors. The present study showed that the multimedia system was more efficient than the virtual reality in reducing the burn patients' pain during dressing. Faber et al. (2011), by investigating the effect of virtual reality on the burn patients' pain during dressing, demonstrated that the burn patients' pain during dressing in the intervention group was significantly less than that in the con-

Table 1. Participants' demographic data

Variable	Levels of variable	Virtual reality	multimedia	control	Statistical test	
Age(year)	Male and female	32 ±8	34±10	39±12	f=0/62	p=0/54
Burn Percentage	Male and female	15±6	15±7	16±6	f=0/45	p=0/65
Gender	Male	(45)9	(70)14	(55)11	x^2=2/62	p=0/5
	Female	(55)11	(30)6	(45)9	df=2	
Education	Under diploma	(95)19	(85)17	(95)19	x^2=5/3	p=0/5
University	(5)1	(5)3	(5)1	df=6		
Palliative	Receive	(75)15	(75)15	(75)15	x^2=0/2	p=1
No receive	(25) 5	(25) 5	(25) 5	df=4		

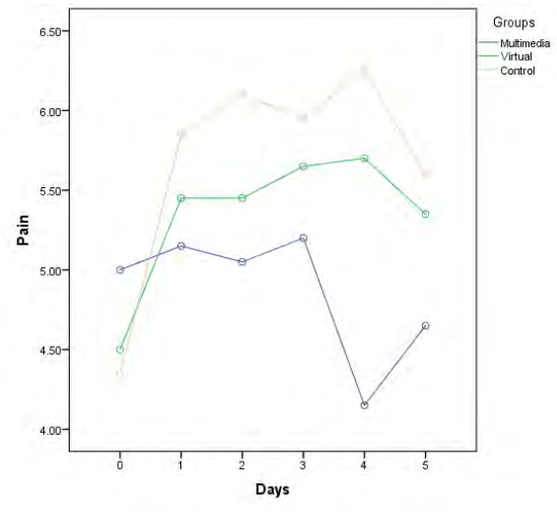

Figure 1. Changes of pain over time in three groups

Table 2. The result of repeated measurements analysis with first measure as a covariat

Variable	Source of variation		Wilks' Λ	F	d.f.	Error df	SS	d.f.	MS	F	P
Pain	Within subjects	Time	0.97	0.33	4	53					0.85
		Group * Time	0.81	1.50	2	90					0.16
	Between Subjects	Group					123.79	1	61.89	5.52	0.006
		Error (between)					627.38	91	11.20		

Table 3. The results of repeated measure analysis on pain score in three groups

Pain	Groups	Mean	Std. Deviation	comparison	p-value	Lower Bound	Upper Bound
Day1	Multimedia	5/15	1/98	M vs V	0/196	-1/594	0/333
	Virtual reality	5/45	1/98	M vs C	0/023	-2/097	-0/161
	Control	5/85	1/72	C vs V	0/301	-1/457	0/458
day2	Multimedia	5/05	2/11	M vs V	0/181	-1/818	0/351
	Virtual reality	5/45	2/35	M vs C	0/008	-2/573	-0/394
	Control	6/10	1/65	C vs V	0/169	-1/827	0/327
day3	Multimedia	5/20	2/54	M vs V	0/136	-1/886	0/263
	Virtual reality	5/65	2/03	M vs C	0/027	-2/299	-0/141
	Control	5/95	1/63	C vs V	0/447	-1/476	0/659
day4	Multimedia	4/15	2/58	M vs V	0/002	-3/097	-0/756
	Virtual reality	5/70	2/12	M vs C	0/00	-3/766	-1/413
	Control	6/25	2/02	C vs V	0/258	-1/826	0/500
day5	Multimedia	4/65	2./71	M vs V	0/10	-2/322	0/208
	Virtual reality	5/35	2/68	M vs C	0/030	-2/685	-0/144
	Control	5/60	1/35	C vs V	0/571	-1/614	0/90

M= Multimedia, V=Virtual reality, C=Control

trol group (6), which was consistent with results of the present study. Similarly, in the present study, virtual reality could reduce the burn patients' pain during dressing, although the reduction was not significant. Moreover, the results obtained by Schmitt et al. (2011) who investigated the effect of virtual reality on the burn patients' pain during dressing were consistent with results of the present study since, in their study, this treatment technique also led to a significant reduction in the patients' pain (17). In another study conducted on effect of the use of virtual reality on control of the infant burn patients' pain during occupational therapy, Hoffman et al. (2009) showed that the virtual reality resulted in the reduced pain of the infant burn patients during occupational therapy, which was consistent with results of the present results (18).

Many other psychological non-pharmacologic methods have been also used for pain relief; in this regard, the multimedia systems can be mentioned, which are PC-like systems composed of LCD and TV with capability of playing digital images and sounds as well as moving pictures that are to some extent similar to the real images (24).For instance, Kaur et al. (2011) conducted a study to determine effectiveness of the multimedia system in reducing pain and distress among children during venipuncture. Their findings indicated the significantly reduced pain during venipuncture in the intervention group watching cartoons (25), which was consistent with results of the present study. Similarly, in the present study, the multimedia system led to a significant reduction in pain intensity. Moreover, Choudhury et al. (2013) investigated the effect of audiovisual distraction on pain relief during ear micro-suction, the results of which indicated that pain in the intervention group was significantly less than the control group, which was consistent with results of the present study (26). As another example, Miguez-Navarro and Guerrero- Marquez (2014) investigated the effect of audiovisual distraction on pain reduction among children aged 3-11 years old. Their findings showed that the pain during venipuncture was significantly reduced in the intervention group watching cartoons, which was consistent with results of the present study (27). The headset, which is specifically used for playing images and sounds of the virtual reality, separated the patient's eyesight from the room, using a small computer screen placed in front of the patient's eyes, blocks the hospital noise using the headset, and replaces the noise with relaxing images and sounds. As a result, once the invasive procedures are performed by the health staff, the patient's attention is distracted from the real world to the virtual world (28). This is based on the assumption that pain perception has a psychological structure, and accordingly human attention is limited and should be focused on the painful stimuli to perceive the pain. Therefore, pain perception is limited when attention of the individuals is distracted from the painful stimuli (29). On the other hand, regarding the fact that a closed space causes claustrophobia and anxiety (21) and since there is a two-way relationship between anxiety and pain, the increased anxiety results in the cycle of pain and anxiety (19, 20). In the same way, by separating the individual from the environment, the virtual reality headset creates a closed space so that the increased anxiety may lead to the increased pain as well as the continued cycle of pain and anxiety. The present study clearly showed that the multimedia system was an appropriate method for reducing the burn patients' pain compared to the virtual reality so that it significantly reduced the pain level; however, due to creating the claustrophobia and anxiety, the virtual reality led to a relative reduction in the pain level.

One of the limitations of the present study was that dressing of the female patients was performed with the help of the female researcher due to the cultural issues as well as the different gender of the researcher, so such a difference in the dressing method might influence results of the study. Moreover, the lack of private room for patients during the intervention, fatigue and stress of the patients during dressing due to the invasive operation, and the sample size limitation due to consideration of the below 25% burns were other factors that could affect the results. To compensate for these limitations at the time of dressing, the patient privacy was kept using a shield; besides, dressing was carried out early on the morning shift when fatigue and stress of patients were less. Since the patients with higher burn percentage were transferred to ICU and also due to the fact that it was impossible to perform sampling of the higher burn percentages in the ward, it is suggested to perform the future studies on the samples with burns of above 25%.

Conclusion

Results of the present study showed that the burn patients' pain during dressing was significantly reduced by the multimedia system method compared to the virtual reality technique, which indicated efficiency of the multimedia system compared to the virtual reality in reducing the burn patients' pain during dressing. On this basis, it is suggested to use this method to control

pain of the burn patients. Furthermore, it is proposed to evaluate this method seriously and precisely in the future studies in order to determine its advantages and disadvantages as well as its costs for the patient and care systems.

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Competing interests

The authors declare that they have no competing interests.

References

1. Harbin KR, Norris TE. Anesthetic management of patients with major burn injury. AANA J. 2012;80(6):430-9.
2. Rowan MP, Cancio LC, Elster EA, Burmeister DM, Rose LF, Natesan S, et al. Burn wound healing and treatment: review and advancements. Crit. care. 2015;19(1):243.
3. Emami S-A, Karimi H, Alijanpour A, Razieh A, Sajedeh. Epidemiology of Contact Burns. MRJMMS. 2015;3(4):126-9.
4. Arif M, Ramprasad K. Prevalence of Anxiety and Depression in Burns Patients in a Tertiary Care Hospital. IOSR-JDMS. 2013;10(4):6-9.
5. He F, Cao R, Feng Z, Guan H, Peng J. The impacts of dispositional optimism and psychological resilience on the subjective well-being of burn patients: A structural equation modelling analysis. PLoS One. 2013;8(12):1-5.
6. Faber AW, Patterson DR, Bremer M. Repeated use of immersive virtual reality therapy to control pain during wound dressing changes in pediatric and adult burn patients. J Burn Care Res. 2013;34(5):563.
7. Small C, Stone R, Pilsbury J, Bowden M, Bion J. Virtual restorative environment therapy as an adjunct to pain control during burn dressing changes: study protocol for a randomised controlled trial. Trials. 2015;16(1):329.
8. de Castro RJA, Leal PC, Sakata RK. Pain management in burn patients. Braz J Anesthesiol. 2013;63(1):149-58.
9. Maani CV, Hoffman HG, Fowler M, Maiers AJ, Gaylord KM, DeSocio PA. Combining ketamine and virtual reality pain control during severe burn wound care: one military and one civilian patient. Pain Med. 2011;12(4):673-8.
10. Morris L, Louw Q. Pain and anxiety experiences of South African adult burn injury patients during physiotherapy management. SAJPA. 2010;66(1):6-9.
11. Aitken BL, Stookey JM, Noble S, Watts J, Finlay D. The effects of an oral distraction on cattle during a painful procedure. Can Vet J. 2013;54(6):588-90.
12. Jameson E, Trevena J, Swain N. Electronic gaming as pain distraction. Pain Res Manag. 2011;16(1):27-32.
13. Hillgrove-Stuart J, Pillai Riddell R, Horton R, Greenberg S. Toy-mediated distraction: Clarifying the role of distraction agent and preneedle distress in toddlers. Pain Res Manag.. 2013;18(4):197-202.
14. Moreno García I, Delgado Pardo G. Intervention Program based on Virtual Reality for Pediatric Burns. Int J Clin Health Psychol. 2013;9(1):41-3.
15. Keefe FJ, Huling DA, Coggins MJ, Keefe DF, Rosenthal MZ, Herr NR, et al. Virtual reality for persistent pain: a new direction for behavioral pain management. Pain. 2012;153(11):2163-6.
16. Malloy KM, Milling LS. The effectiveness of virtual reality distraction for pain reduction: a systematic review. Clin Psychol Rev . 2010;30(8):1011-8.
17. Schmitt YS, Hoffman HG, Blough DK, Patterson DR, Jensen MP, Soltani M, et al. A randomized, controlled trial of immersive virtual reality analgesia, during physical therapy for pediatric burns. Burns. 2011;37(1):61-8.
18. Hoffman HG, Meyer III WJ, Ramirez M, Roberts L, Seibel EJ, Atzori B, et al. Feasibility of articulated arm mounted Oculus Rift Virtual Reality goggles for adjunctive pain control during occupational therapy in pediatric burn patients. Cyberpsychol Behav Soc Netw. 2014;17(6):397-401.
19. Richardson P, Mustard L. The management of pain in the burns unit. Burns. 2009;35(7):921-36.
20. Park E, Oh H, Kim T. The effects of relaxation breathing on procedural pain and anxiety during burn care. Burns. 2013;39(6):1101-6.
21. Lourenco SF, Longo MR, Pathman T. Near space and its relation to claustrophobic fear. Cognition. 2011;119(3):448-53.
22. Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual analog scale for pain (vas pain), numeric rating scale for pain (nrs pain), mcgill pain questionnaire (mpq), short-form mcgill pain questionnaire (sf-mpq), chronic pain grade scale (cpgs), short form-36 bodily pain scale (sf-36 bps), and measure of intermittent and constant osteoarthritis pain (icoap). Arthritis Care Res . 2011;63(11): 240-52.
23. Mazlom SR, Hosseini Amiri M, Tavoosi SH, Manzari ZS, Mirhosseini H. Effect of direct transcranial current stimulation on pain intensity of burn dressing. Evidence Based Care Journal. 2015;4(4):35-46. Persian.
24. Morris T. Multimedia systems: Delivering, generating and interacting with multimedia: Springer Science & Business Media.2012.1-2p.
25. Kaur B, Sarin J, Kumar Y. Effectiveness of cartoon distraction on pain perception and distress in children during intravenous injection. IOSR-JNHS. 2014; 3(3): 35-46.
26. Choudhury N, Amer I, Daniels M, Wareing M. Audiovisual distraction reduces pain perception during aural microsuction. Ann R Coll Surg Engl. 2013;95(1):34-6.
27. Miguez-Navarro C, Guerrero-Marquez G. Video-Distraction System to Reduce Anxiety and Pain in Children Subjected to Venipuncture in Pediatric Emergencies. Pediatric Emerg Care Med. 2014; 1(1): 1-8.
28. Hoffman HG, Chambers GT, Meyer WJ, Arceneaux LL, Russell WJ, Seibel EJ, et al. Virtual reality as an adjunctive non-pharmacologic analgesic for acute burn pain during medical procedures. Ann. Behav Med . 2011;41(2):183-91.
29. Li A, Montaño Z, Chen VJ, Gold JI. Virtual reality and pain management: current trends and future directions. Pain Manag . 2011;1(2):147-57.

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The effect of exercise during hemodialysis on fatigue and self-efficacy in patients: a blind randomized clinical trial

Kobra Parvan[1], Farank Jabar-Zadeh[1], Parvin Sarbakhsh[2], Ebrahim Akhtari-Shojai[3], Tahereh Zarei[4]
[1]Department of Medical-Surgical Nursing, Faculty of Nursing and Midwifery, [2]Department of Health and Nutrition, Faculty of Health and Nutrition, [3]PhD in Exercise Physiology, Department of Emam Reza Hospital, [4]Graduate student of Nursing (internal surgery), Faculty of Nursing and Midwifery, Tabriz University of Medical Sciences, Tabriz, iran

Abstract

Aim: Due to the increased prevalence of chronic diseases such as kidney failure, physical, mental and social needs of these patients have also increased and their well-being seems essential. The aim of this study was to investigate the effects of exercise during hemodialysis on fatigue and self-efficacy of hemodialysis patients. Method and Material: This study is a clinical trial; study sample consisted of 46 patients undergoing hemodialysis and who had referred to hemodialysis center of Sahid Madani Hospital in Tabriz; availability sampling method had been used based on the inclusion criteria and with a consent for participating in the study; the sample had been selected from research population and have been divided randomly into two groups of control and experiment. The measuring tools for collecting data included Fatigue Severity Scale (FSS) and Sherer General Self-efficacy scale (SGSES) which were used after determining validity and reliability. After collecting data, the results had been analyzed using SPSS 20 software. For describing quantitative data, the symmetry of the mean and standard deviation had been used and for qualitative data, frequency and percentage had been used and for comparing two groups, analysis of covariance had been used. Results: The results of the current study showed that all patients with chronic renal failure suffered from fatigue and their self-efficacy decreased. Self-Efficacy in patients from the experiment group significantly increased, but it was not significant (p-value = 0.06) and after treatment, fatigue was significantly reduced in the intervention group (p-value <05). Discussion: The results of this study showed that exercising during hemodialysis not only reduces fatigue of these patients, but also leads to improvement of self-efficacy and exercise is recommended in dialysis centers.

Keywords

Hemodialysis; Fatigue; Self-Efficacy; Sports

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Corresponding Author: Tahereh Zarei, Graduate student of Nursing (internal surgery), faculty of Nursing and Midwifery, Tabriz University of Medical Sciences, Tabriz, iran. E-Mail: nursezarei@yahoo.com

Introduction

The most prominent event on the eve of the twenty-first century which health communities and faculties face is the prevalence of chronic diseases. Kidney failure is one of the common diseases of mankind which 2 to 3 percent of people worldwide suffer from this disease. (1) The prevalence of chronic kidney failure in the world was 242 cases per million which increases each year (2). Worldwide, the incidence of kidney disease is growing steadily at a rate of 6% (3). Annual statistics of hemodialysis patients in Iran is increasing by 15% (4). The number of patients with end stage of renal failure was around 3 million and 200 thousand at the end of 2013. At the end of 2013, 2 million 250 thousand individuals used hemodialysis treatment and 272 thousand used peritoneal dialysis; and the number of patients who received transplant was also about 678 thousand people. Dialysis Community of Iran have estimated the number of dialysis patients at the end of 2014 to be about 26,500 people which approximately 25 thousand of these individuals (94%) are undergoing hemodialysis treatment and a thousand and 450 individuals are benefited from peritoneal dialysis (2). According to the Support Society for kidney patients of East Azarbaijan province, now there are about 1524 dialysis patients in the province (3).

Hemodialysis is the most common method of Dialysis and the major purpose for this treatment is to try and make the life of kidney failure patients similar to normal life as much as possible (4). Several studies reported that patients undergoing hemodialysis have less physical ability and capacity comparing to normal people which is due to anemia, impaired blood flow through distal limbs, body edema, reduced cardiovascular function, depression and malnutrition, and so on (5). One of the main points in treating hemodialysis patients is to maximize their performance and welfare, which refers to the ability of performing daily activities and to feel good (6). Physical exercises, as one of the treatment options and accessories can be used in dialysis patients which leads to beneficial effects on physical, psychological and social problems and it is a way to maintain stamina and physical performance and help improve quality of life; not only has personal benefits, but it also has social benefits such as reducing the cost of health and social cares (7).

Fatigue is one of the most annoying and most severe symptoms reported by hemodialysis patients (8). Physiological factors include anemia, age and body size, malnutrition, uremia, high cholesterol levels and treatment-related factors and personal characteristics are some causes of fatigue in these patients (9). Fatigue reduces well-being in these patients and it has several various effects on physical, emotional and cognitive aspects (10).

Exercise is beneficial for patients with kidney failure who have fatigue and limit daily functioning. Since hemodialysis patients spend much time in dialysis centers, sport programs during dialysis have many advantages such as saving time as well. Exercise during dialysis increases functional capacity. However, improvement in functional capacity, physical activity and fatigue are not guaranteed. Nurses have an important role in improving the quality of life, the need for security, cost and availability of services, and the exercixes which patients are able to do (11).

One of the most important factors in improving the quality of life in hemodialysis patients is self-efficacy which means the confidence in one's ability for performing self-care behaviors in certain circumstances (12). Studies show individuals who are confident in their abilities, participate more actively in health improvement programs (13). Correlational studies show that increased self-efficacy is correlated with adherence to treatment, health improvement and reduction of physical and psychological symptoms; and inability to adapt to the disease may lead to negative consequences such as non-compliance with treatment (14). According to studies, changes in sport behavior in many chronic diseases have led to an increase in self-efficacy (15). However, in patients with ESRD, little research has examined the relationship between exercise and self-efficacy. Nurses have an important and effective role in promoting self-care, self-efficacy, compliance, continuity and coping with the disease; and they also have a multi-dimensional role in helping patients with chronic diseases to achieve the highest performance with lowest level of symptoms (16). Therefore, current study aimed to investigate the effects of exercise during hemodialysis on fatigue and self-efficacy of hemodialysis patients.

Material and Method

This study is a clinical trial with registration code of IRCT2016063028715N1; the study population included hemodialysis patients who referred to hemodialysis center of Shahid Madani hospital. For determining the sample size, the basic information for calculating the effect size had been extracted form a study by Hadian et al. (17); a certainty degree of 95% and a test power of 90% had been considered; 17 participants had been calculated for each group as the minimum sample size by considering 16.73 units for variability of intervention for fatigue variable and with the use of Pukak formula. Considering 30% downfall, the sample sized was increased to 23 cases in each group.

The data collection tools included: Fatigue Severity Scale (FSS) and Sherer General Self-Efficacy Scale (SGSES). Also, demographic characteristics included age, sex, marital status, level of education, employment status, and years of dialysis and history of other diseases. Fatigue Severity Scale (FSS) has 9 questions and each question is based on the Likert scales, ranging from strongly disagree to strongly agree. For scoring, each item is scored from 1 to 7, low scores indicate less fatigue and high scores indicate high fatigue. The maximum score that a person can obtain in this scale is 63 and a minimum score is 9. Fatigue Severity Scale had been developed by Krupp et al. (1989) and the reliability of this scale in Iran had been approved by Farahani et al (1391), which internal consistency of items for "Fatigue Severity Scale" had been calculated as 0.96 using Cronbach's alpha coefficient, which shows that the items of the questionnaires assess one concept. After correcting for overlaps, the correlation of each item with another was higher than desired level of 0.4. ICC coefficient for investigating the relative repeatability of Persian version of the Fatigue Severity Scale was 0.93 which was higher than the acceptable level of 0.7 (18). Sherer General Self-efficacy Scale (SGSES) measures individuals' beliefs and ability to overcome different situations; this scale has 17 questions and each question is based on the Lik-

ert scales, ranging from strongly disagree to strongly agree. For scoring this scale, each item receives a score from 1 to 5. Question 1, 3, 8, 9, 13 and 15 are scored from right to left and the rest of the questions are reversed, meaning that they are scored from left to right. Therefore, maximum score that a person can obtain in this scale is 85 and the minimum is 17. This scale had been developed by Sherer and Maddox (1982) and it has been translated and validated by Barati (1996); based on Cronbach's alpha, reliability coefficient for the subscales of general self-efficacy and social self-efficacy had been reported to be 0.86 and 0.71 respectively. The reliability of this test had been reported as 0.70 based of Spearman-Brown correlation and 0.76 using split method of Gottman (19).

The reliability of the questionnaires had been studied after completion by 20 hemodialysis patients within two weeks; the internal consistency for fatigue scale had a Cronbach's alpha 0f 0.89 and reliability over time (intra-group correlation) for the same questionnaire had ICC coefficient 0f 0.99. Moreover, the internal consistency of Self-efficacy questionnaire had a Cronbach's alpha of 0.87 and reliability over time (intra-group correlation) for self-efficacy questionnaire had ICC coefficient of 0.99.

The patients had been selected base on availability method and inclusion criteria, and they had been randomly assigned into two groups of control and experiment. Randomized blocking was also included in the analysis. Inclusion criteria included: age over 18 years, history of hemodialysis for at least 6 months, lack of physical limitations in self-care, lack of orthopedic problems that prevent exercising, lack of any regular sport programs in past six months, lack of cardiovascular disease, shortness of breath and severe heart failure based on the approval of specialist physician and patient's records which prevent them from any exercise program, minimum ability to read and write, willingness to participate in a sports program and an informed consent. Exclusion criteria included: receiving a kidney transplant during the study, having incurable disease (cancer, AIDS, and so on), not wanting to continue in the study, repeated drop of blood pressure to less than 50/90 or severely elevated blood pressure over than 90 / 160 during the intervention, and shortness of breath and chest pain during exercise.

Then, self-efficacy and fatigue have been assessed in both groups using questionnaires. Participants in the intervention group received an eight week exercise program which including pedal bicycle during hemodialysis in the dialysis center and under the supervision of medical doctors specializing in exercise physiology. Before starting the exercise, vital signs (blood pressure, pulse and respiration) had been measured in all patients. Exercise program included pedal bicycling based on proposed sport activities for ESRD individuals; which consisted of 3 days per week, and each session was about 30 to 60 minutes in the first two hours of hemodialysis (20-25). Also during cycling vital signs of patients had been monitored every 15 minutes and if there was a rise or drop of blood pressure, the exercise would be stopped. The speed of cycling had been adjusted according to the physical ability of patients; it started from 30 RPM and based on heart rate and vital signs of patients, it increase to 60 RPM in the last weeks of the program. Exercising on stationary bicycles had been performed which is designed for individuals who are lying on the dialysis bed. Cycling exercise had been selected because it is safe and doable during dialysis; in addition, the patient learns easily how to work with the device. After 8 weeks of exercise, fatigue and self-efficacy of patients had been assessed in both control and experiment groups using questionnaires. We did not have sample loss during the study. The bicycles were handmade customized specifically for dialysis center of Shahid Madani learning hospital of Tabriz which is approver by physicians and the physical education department of University of Tabriz. The diameter of the wheels was 20 cm, the distance from the wheel to pedals was 21 cm and pedal size was 10 × 8 cm.

After collecting data from all subjects, results had been analyzed using SPSS 20 software. To describe the quantitative data, symmetrical mean and standard deviation had been used; and for qualitative data, frequency and percentage had been used. Analysis of covariance had been used for the comparison of quantitative variables between the two groups at the beginning and end of the study.

Results

The study sample included 46 patients undergoing hemodialysis at Shahid Madani Hospital of Tabriz; 23 patients assigned to intervention group which consisted of 18 men and 5 women, and 23 patients were assigned to control group which consisted of 18 men and 5 women; the demographic information is shown in Table 1.

After the intervention, and obtaining the data, the normality of self-efficacy and fatigue had been studied with the use of drawing histograms and the Kolmogorov-Smirnov test and after their normality had been approved, covariance analysis (to adjust confounding) had been used to evaluate the effect of intervention on self-efficacy and fatigue. After the intervention, mean scores for fatigue in both experiment and control groups had decreased as it can be seen in table 3; and this declination was greater for the experiment group. Mean scores for self-efficacy increased in both experiment and control groups after intervention as it can be seen in table 3; moreover, the inclination was higher in experiment group. Although, the two groups did not have any significant differences for self-efficacy and fatigue confounding factors, age, gender, level of education (table 1), the comparison between two groups using covariance analysis and considering confounding variables for each person for age, sex, and level of education in self-efficacy and fatigue had been performed, and self-efficacy of patients had increased in experiment group, but it was not significant (P-value = 0.06); also fatigue was significantly lower in experiment group after intervention (p-value <05) (Table 3).

Table 1) demographic data of participants in the study as distinguished in intervention and control groups

(Quantitative data had been reported as mean and standard deviation, and qualitative data as frequencies and percentages.)

Tale 2) comparing mean scores for self-efficacy and fatigue before and after intervention

For comparison the mean scores for fatigue and self-efficacy, covariance analysis had been performed before and after the intervention for both control and experiment groups which showed significant results.

Table 1.

	Variable Frequency	Control Group		Experiment Group		Sum of Frequencies	Sum of Percentages
		Percentage - Mean	Frequency		Percentage - Mean		
Sex	Male	5	21.7	5	21.7	10	21.7
	Female	18	78.3	18	78.3	36	78.3
Marital Status	single	1	4.3	1	4.3	2	4.3
	Married	14	60.9	18	78.3	32	69.6
	Divorced	8	34.8	4	17.4	12	26.1
Education	elementary	18	78.3	17	73.9	35	76.1
	junior school	4	17.4	1	4.3	5	10.9
	Diploma	1	4.3	2	8.7	3	6.5
	university	0	0	3	13	3	6.5
Employment Status	unemployed	8	34.8	3	13	11	23.9
	house wife	5	21.7	5	21.7	10	7.21
	Farmer	2	8.7	0	0	2	4.3
	self-employed	4	17.4	7	30.4	11	23.9
	retired	4	17.4	8	34.8	12	26.1
Economic Status	less income than expense	16	69.6	17	73.9	33	71.7
	More income than expense	7	30.4	6	26.1	13	28.3
Disease History	Diabetes	6	26.1	7	30.4	13	28.3
	Hypertension	9	39.1	5	21.7	14	30.4
	Non	8	34.8	11	47.9	19	41.3
Age (Year)		23	60.17±10.52	23	89.04±9.51	46	-
History of Hemodialysis (year)		23	3.91±1.97	23	4.04±2.20	46	-

Table 2.

Variable	Groups	Number	Minimum	Maximum	Mean
Fatigue	Before Intervention	46	20	63	49.30±10.55
	After Intervention	46	18	61	45.02±11.45
Self-Efficacy	Before Intervention	46	20	81	52.67±15.77
	After Intervention	46	32	85	57.34±14.93

Table 3) comparing the mean scores for fatigue and self-efficacy before and after the intervention for both control and experiment groups

Conclusion

The results of the current study showed that exercising with a stationary bicycle during hemodialysis for 8 weeks and three times a week reduced the fatigue of patients undergoing hemodialysis and increases self-efficacy of these patients; consistent with the results of the current study, a study in Tehran in 2014 by Zeinab Motedayen and colleagues studied the effects of exercise on fatigue of patients; the sample included 66 hemodialysis patients that had been randomly divided into experiment and control groups. The experiment group received an exercise program twice a week for two months. Fatigue of patients had been measured using FSS before and after the exercise program in both groups of experiment and control. Fatigue of patients in the experiment group increased significantly comparing to control group after the exercise program ($p < 0.05$))26). Another study by Riahi and colleagues at the dialysis center of Shariati in Isfahan that was conducted in 2013, studied the effects of exercise on quality of life and muscle strength in hemodialysis patients. This studies was experimental with pre-test and post-test and with both experiment and control groups. The results of this study showed quality of life of these patients had improved significantly ($p>0.05$) after 5 months of exercis-

Table 3.

Variable	Group		Number	Mean	Difference of two groups	Lower limit of 95% confidence interval for the difference	Higher limit 95% confidence interval for the difference	p-value
Fatigue	before intervention	control	23	48.78±9.79	1.043	-5.295	7.382	0.74
		experiment	23	49.82±11.47				
	After intervention	control	23	48.39±9.49	-6.739	-13.312	-0.165	0.04
		experiment	23	41.65±12.43				
Self-efficacy	before intervention	control	23	51.95±16.25	1.434	-8.035	10.904	0.76
		experiment	23	53.39±15.60				
	After intervention	control	23	53.26±14.60	8.173	-0.450	16.798	0.06
		experiment	23	61.43±14.25				

ing while the control group had not any significant inclination; also muscle strength in the experiment group had a significant increase comparing to control group ($p < 0.05$). The results of this study showed that exercise training had an effect on quality of life and fatigue and improve muscle strength in hemodialysis patients. (27)

A study in California in 2008 had been conducted by Cynthia K. Straub et al., and studied the effects of exercise in fatigue management of peritoneal dialysis patients; the sample included 14 patients undergoing peritoneal dialysis. In this study, patients received exercising programs for 3 or 4 times a week for 2 months and each session were about 30-minutes; exercise program included walking, cycling and swimming. Based on the results of this study, there was no significant change in fatigue of the patients after exercise (28). The sample size was probably low in this study which our study had solved this problem.

In a study that was conducted in 2010 in Canada by Hilary Anna Felice, they investigated the effects of exercise during hemodialysis on self-efficacy and physical activity of these patients. Samples of this study included 8 cases of hemodialysis patients that had been divided randomly into experiment and control groups; the experiment group received exercise on stationary bicycles for 60 minutes in the first 2 hours of hemodialysis; exercise continued for 8 weeks, 3 times week. The results showed, after 8 weeks, no significant changes had observed in self-efficacy and physical activity. And at the end, the authors recommend a repeated study with a larger sample (29). The current study had been conducted with 46 samples, and the results showed significant impact of exercise on improving self-efficacy in hemodialysis patients after 8 weeks of bicycle exercise ($p<0.001$).

In a study that had been conducted in Australia in 2013 by Fiona Barnett, they investigated the effect of exercise on activity and self-efficacy in older women and young people; the samples included 25 young women with an average age of 19 years; and 25 older women with an average age of 57 years. The results showed that all patients with chronic renal failure complications suffered from fatigue and loss of self-efficacy, and this fact indicates the importance of fatigue and self-efficacy and its impact on all aspects of life in these patients; therefore, fatigue and reduced self-efficacy may have devastating effects; although with fatigue being one of the most important signs and symptoms of the disease, exercise and rehabilitation can be considered as noninvasive and easily performed method should gain the attention of care-givers for using it.

Among all sports, exercising with stationary bicycles can be one of the best physical activities for hemodialysis patients due to its convenience usage for the patient and its controllability for nurses during hemodialysis. Other advantages of regular exercise are increased strength, improvement of posture, reduced fatigue, and improvement of mood, increased confidence and general well-being and so on. Doing physical exercises increase the autonomy of the individual and not only leads to improvement of quality of life but also affects balance of the person, upper and lower limb coordination and prevents cardiovascular disease (31).

Conclusion

The results of this study shows positive effects of exercise during hemodialysis in improving self-efficacy and reduce fatigue in hemodialysis patients, so exercise during hemodialysis can be considered as a routine and effective program by supervision of medical staff in hemodialysis centers, and due to its low cost and availability, this method is a step to reduce the suffering of patients undergoing hemodialysis.

Study Limitations

The limitation of this study was that fatigue and self-efficacy are mental phenomena and measuring them is very difficult and is affected by many variables such as emotional changes and other uncomfortable Symptoms accompanied with chronic disease, therefore, careful consideration is difficult and controlling these aspects was out of reach of reaserchers.

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References

1. Rambod M, Rafiei F. Relationship between perceived social support and quality of life in hemodialysis patients. J Nurs Scholarsh. 2010;42(3):242-9.
2. WWW.irankf.org.
3. www.e-az-kidney.com/index.php/2013-06-19-09-58.
4. Murea M, James KM, Russell GB, Byrum GV, Yates JE, Tuttle NS, et al. Risk of catheter-related bloodstream infection in elderly patients on hemodialysis. Clinical Journal of the American Society of Nephrology. 2014;9(4):764-70.
5. Beto J. Improving first-year mortality in patients on dialysis: a focus on nutrition and exercise. Nephrology Nursing Journal. 2010;37(1):61.
6. Sayin A, Mutluay R, Sindel S, editors. Quality of life in hemodialysis, peritoneal dialysis, and transplantation patients. Transplantation proceedings; 2007: Elsevier.
7. Chojak-Fijałka K, Smoleński O, Michałowski A, Piotrowski W. The effects of 6-month physical training conducted during hemodialysis in ESRD patients. Med Rehabilit. 2006;10:25-41.
8. Schneider RA. Chronic renal failure: assessing the Fatigue Severity Scale for use among caregivers. Journal of clinical nursing. 2004;13(2):219-25.
9. Pagels A, Heiwe S, Hylander B. Nutritional status and handgrip strength in predialysis patients. Journal of renal care. 2006;32(3):151-5.
10. Moghadasian S, Hagh MHS, Hokmabadi LA. Lifestyle of Hemodialysis Patients in Comparison with Outpatients. Journal of caring sciences. 2012;1(2):101.
11. Takhreem M. The effectiveness of intradialytic exercise prescription on quality of life in patients with chronic kidney disease. The Medscape Journal of Medicine. 2008;10(10):226.
12. Smaeli M, Alikhani M, Hosseini F. The quality of life and self efficacy of the patients under hemodialysis. Iran Journal of Nursing. 2005;18(41):77-84.
13. Bandura A. Self-efficacy: The exercise of control: Macmillan; Worth Publishers, 1997.
14. Tsay SL. Self-efficacy training for patients with end-stage renal disease. Journal of Advanced Nursing. 2003;43(4):370-5.
15. Carlson JJ, Norman GJ, Feltz DL, Franklin BA, Johnson JA, Locke SK. Self-efficacy, psychosocial factors, and exercise behavior in traditional versus modified cardiac rehabilitation. Journal of Cardiopulmonary Rehabilitation and Prevention. 2001;21(6):363-73.
16. Quinan P. Control and coping for individuals with end stage renal disease on hemodialysis: a position paper. CANNT journal= Journal ACITN. 2006;17(3):77-84.
17. HADIAN JZ, Aliasgharpoor M. Evaluating the effects of designed exercise program on mean of activity tolerance in hemodialysis patients. 2012.
18. Shahvaroughi FA, Azimian M, Falahpour M, Karimlou M. Fatigue Severity Scale (FSS): Evaluatiopn of Reliability of the Persian Version among Persons with Multiple Sclerosis. 2010.
19. Barati SB. Examine the relationship between the work of simple and multiple variables, self-esteem and self-discovery with academic performance in third grade students new system Ahvaz graduate thesis in General Psychology, Faculty of Education and Psychology, Shahid Chamran University. 1376.
20. Johansen KL. Exercise in the end-stage renal disease population. Journal of the

American Society of Nephrology. 2007;18(6):1845-54.
21. Jang E-J, Kim H-S. Effects of exercise intervention on physical fitness and health-relalted quality of life in hemodialysis patients. Journal of Korean Academy of Nursing. 2009;39(4):584-93.
22. van Vilsteren MC, de Greef MH, Huisman RM. The effects of a low-to-moderate intensity pre-conditioning exercise programme linked with exercise counselling for sedentary haemodialysis patients in The Netherlands: results of a randomized clinical trial. Nephrology Dialysis Transplantation. 2005;20(1):141-6.
23. Cheema BSB, Smith BCF, Singh MAF. A rationale for intradialytic exercise training as standard clinical practice in ESRD. American Journal of Kidney Diseases. 2005;45(5):912-6.
24. Johansen KL. Exercise and chronic kidney disease. Sports medicine. 2005;35(6):485-99.
25. Parsons TL, Toffelmire EB, King-VanVlack CE. Exercise training during hemodialysis improves dialysis efficacy and physical performance. Archives of physical medicine and rehabilitation. 2006;87(5):680-7.
26. Motedayen Z, Nehrir B, Tayebi A, Ebadi A, Einollahi B. The Effect of the Physical and Mental Exercises During Hemodialysis on Fatigue: A Controlled Clinical Trial. Nephro-urology monthly. 2014;6(4).
27. Riahi Z, Esfarjani F, Marandi SM, Kalani N. The effect of intradialytic exercise training on the quality of life and fatigue in hemodialysis patients. Journal of Research in Rehabilitation Sciences. 2012;1(1):219-27.
28. Straub CK, Murphy SO, Rosenblum R. Exercise in the management of fatigue in patients on peritoneal dialysis. Nephrology Nursing Journal. 2008;35(5):469.
29. Felice H. The Effects of an Intra-Dialytic Exercise Program on Self-Efficacy and Physical Activity: A Pilot Study. 2010.
30. Barnett F. The effect of exercise on affective and self-efficacy responses in older and younger women. Journal of Physical Activity and Health. 2013;10(9)12.
31. Schapiro RT. Managing symptoms of multiple sclerosis. Neurologic clinics. 2005;23(1):177-87

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The fluctuation of BRCA1 gene is associated in pathogenesis of familial colorectal cancer type X

Colorectal cancer

Mahdieh Nejadtaghi[1], Effat Farrokhi[1], Ali Akbar Samadani[2], Mehrdad Zeinalian[3], Morteza Hashemzadeh-Chaleshtori[1]
[1]Cellular and Molecular Research Center, Shahrekord University of Medical Science, Shahrekord,
[2]Faculty of Medicine, Research center of Physiology, Cancer Research Center, Semnan University of Medical Sciences, Semnan,
[3]Department of Genetics & Molecular biology, School of Medicine Isfahan University of Medical Sciences, Isfahan, Iran

Abstract

Aim: Among families fulfilling the Amsterdam criteria HNPCC, nearly 40 % of this cases are microsatellite stable and not DNA mismatch repair gene (MMR) and also these mutations were found in this situation. Correspondingly, these families were nominated as familial colorectal cancer type X (FCCTX). The BRCA1 gene plays a role in main cellular pathways and germ line mutations in this gene could underlie different familial cancers. Material and Method: In this way, samples were selected according to previous study that patients who met Amsterdam criteria for lynch syndrome but did not have defective MMR gene and are known as FCCTX. So, 25 normal tissues have been considered for further studies and HRM method was used in order to detect mutations in 2, 3,5,16 and 20 exons of the BRCA1gene. Results: For all samples, the DNA was tested by HRM for the detection of mutations in BRCA1 exons. After normalization and temperature shifting, a clear difference was evident between the melt curves for each sample. Through the different samples of each group, one was selected for sequencing. Based on our sequencing results deleterious BRCA1 gene mutations were not identified and there was no significant difference between the sequences of the samples with a different melting curve. Discussion: Conclusively,our study showed that although BRCA1 is a critical gene playing role in several CRCs, it maybe plays an insignificant role in this type of CRC.

Keywords

FCCTX; HNPCC; Lynch Syndrome; BRCA1; HRM

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Corresponding Author: Effat Farrokhi, Cellular and Molecular Research Center, Shahrekord University of Medical Science, Shahrekord, Iran. Postal code: 8814683991
T.: +98 38 33346692 F.: +98 38 33330709 E-Mail: e_farrokhi_k@yahoo.com

Introduction

Colorectal cancer (CRC) is the third most common cancer in males and second most common cancer in females worldwide[1]. Inherited elements have a critical role in at least one third of all CRCs [2]. Hereditary nonpolyposis colorectal cancer (HNPCC) is one of the most common inherited CRC syndromes, due to mutations in a DNA mismatch repair gene [3,4].

Among families fulfilling the Amsterdam criteria HNPCC, nearly 40 % of them are microsatellite stable and not DNA mismatch repair gene (MMR) mutations were found among them. These families were nominated as familial colorectal cancer type X (FCCTX) [5]. Individuals with FCCTX display diminished risk for extracolonic neoplasms, and tumorogenesis process tends tend to occur later in life[6,7]. An ambiguity in the nature of the disease for FCCTX presents considerable challenges in terms of deciding upon the best approach to interrogate its genetic basis [8].

The *BRCA1* gene plays a role in numerous main cellular pathways, including checkpoint activation, DNA damage repair, and chromatin remodeling. It seems that the *BRCA*1 tumor suppression function is related to its function in homologous recombination damage repair [9].

Germline mutations in this gene could underlie different familial cancers[8], for example in addition to breast and ovarian cancer its role in prostate, pancreatic and stomach cancers was seen [10]. A recent prospective study of 7015 women with *BRCA1* mutation recognized fivefold increased risk of colorectal cancer among BRCA1 mutation carriers younger than 50 years [11].

In this study, in order to identify new mutations in genes involved in FCCTX, we focus on *BRCA1* gene.

In the present study, we have analyzed mutations in some hot spot exons of the *BRCA1* gene by High Resolution Melting (HRM) technique. HRM consists of the accurate checking the alteration in fluorescence caused by the release of an intercalating DNA dye from a DNA duplex as it is denatured by increasing temperature [12]. This technique has been developed recently and displays great potential for scanning germline and somatic mutations[13].

Matherial and Method

Sample collection and preparation

The Samples were collected from Poursina Hakim Research Center, a referral gastroenterology clinic in central part of Iran, Isfahan. Samples were selected according to previous study that patients who met Amsterdam criteria for lynch syndrome but did not have defective MMR gene [14]. Out of 219 patients who were under 50 years at diagnosis, 45 HNPCC families were selected meeting AC-1 for lynch syndrome. From those, 25 families that did not have defective MMR gene and were known as colorectal cancer type X were selected. The normal tissues of these patients have been considered for further studies. 10µm thickness sections were prepared from 25 samples using microtome.

Mutation screening by HRM

DNA extraction was performed using DNA FFPE Tissue Kit (Qiagen, Hilden, Germany), according to the manufacturer's protocol. DNA concentration and purity were measured by UV spectrophotometry using Nanodrop 2000 (Thermo Fisher Scientific, Waltham, MA, USA).

In this study, we used HRM method to detect mutations in some exons of the *BRCA1* gene. We investigated five *BRCA1* hot spot exons included 2, 3,5,16 and 20 exons.

Designing primer for HRM needs certain special attention for instance, because DNA derived from FFPE is often degraded. Primers were designed by beacon designer software. Primer sequences and amplicon size are given in table 1.

PCR conditions and HRM assay

PCR and HRM analysis was performed in 0.1ml tubes on the Rotor-Gene 6000 (Corbett Research, Sydney, Australia). All samples were tested in duplicate and one negative DNA control was included in each experiment. 10 ng of DNA was amplified in a final volume of 10 ml containing Type-it HRM PCR Kit (Qiagen, Hilden, Germany), forward primer, reverse primer and nuclease free H2O.

PCR cycling parameters were according to the following conditions: initial denaturation at 95°C for 5 min; 45 cycles of 95°C for 15 seconds, 60°C for 25 seconds and 72°C for 25 seconds. The final melting program was melting from 70°C to 90 C, with a ramp of 0. 2°C per second. The cycling and melting conditions for all exons were the same.

These experiments have been done on all of 25 normal tissues. Results were analyzed as fluorescence versus temperature graphs by accompanying Gene Scanning software (v1.7). With normalized, temperature-shifted melting curves displayed as difference plot. Those samples showed a different melting curve were sequenced.

Ethical approval

This study was conducted on samples utilized in previous study and ethical approval process has been already explained in the

Table 1. Primer sequences for HRM

Exon	Primer sequence	Amplicon size
2	F: GTGTTAAAGTTCATTGGAACAGAAAG R: CATAGGAGATAATCATAGGAATCCCA	162
3	F: AGTCATAACAGCTCAAAGTTGAAC R: TGGAGCCACATAACACATTCA	187
5	F: TTCATGGCTATTTGCCTTTTGAG R: TGCTTCCAACCTAGCATCATTAC	193
16-1	F: ATTAAACTTCTCCCATTCCTTTCAG R: TATGAGCAGCAGCTGGACTC	205
16-2	F: GCTGCTGCTCATACTACTG R: TCCAGAATGTTGTTAAGTCTTAGT	198
20	F: TCCTGATGGGTTGTGTTTGG R: TGGTGGGGTGAGATTTTTGTC	157

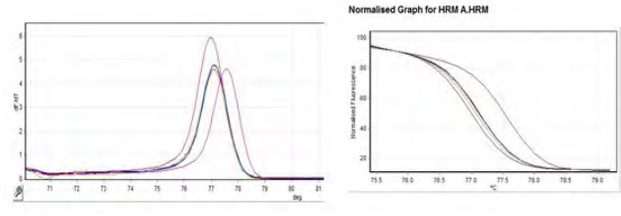

Figure 1. Melting curve and Normalized HRM difference graph of exon 2

previous study (22).Ethical approval was received from the Medical ethics committee of Shahrekord University of Medical Sciences (Research project Number: 91-01-70-1364) and informed consent was obtained.

Result

The DNA extracted from normal tissues of 25 FCCTX samples were tested by HRM for the detection of mutations in some exons of *BRCA*1 gene. After normalization and temperature shifting, a clear difference was evident between the melt curves for each exon. The samples that showed a different melting curve in comparison to others, were categorized in different groups. Then through the different samples of each group, one sample was selected for sequencing.

Based on our sequencing results deleterious *BRCA1*gene mutations were not identified. There was no significant difference between the sequences of the samples with a different melting curve. The result of one of the investigated exons (exon2) was shown in figure 1. The results of other exons were similar (data not shown). Other information available.

Discussion

Since the genetic etiology for FCCTX is largely unknown, genetic confirmation of the diagnosis can help direct surveillance recommendations for the patient and their at-risk family members[15].

BRCA1 gene has high tumor heterogeneity and the role of its mutations in numerous cancers specially in CRCs is a probable event [16,17].

For our purpose HRM has been used as a rapid screen for identifying BRCA1 mutations, finally, after comparing melting curves and analyzing sequencing results, our study showed that there is not any association between the *BRCA1* exons 2, 3,5,16 and 20 mutations and FCCTX. This finding is in contrast to same studies which done about the role of *BRCA1* mutations in other CRCs.

For example, in a study by Phelan C et al 7015 women with a *BRCA*1 mutation were followed in order to detect new cases of colorectal cancer. They showed that twenty-one incident colorectal cancer cases were discovered among all mutation carriers and there was a substantial fivefold increased risk of colorectal cancer among *BRCA1* mutation carriers younger than 50 years [18]. Also in the studies done in the Breast Cancer Linkage Consortium the authors reported modest but significant increases in colorectal cancer risk in family members of families with a *BRCA1*or a *BRCA2*mutation. The relative risk associated with a *BRCA1*mutation was 2.03 [19,20].

There are also some studies, showing a probable role for BRCA1 in colon cancer in the animal models, for example, it has been shown that mice deficient in *BRCA1* will be affected by a varied range of carcinomas, frequently breast and lung but also gastric, endometrial and colon cancer [21].

In the investigated exons we did not find any mutation in FCCTX patients. It can be due to the limited number of samples. Our samples obtained from the screening of 219 CRC patients and only 25 samples remained, which represents FCCTX. On the other hand the mutations in other exons of the *BRCA1* gene may be involved in causing disease. We investigated hot spot exons and it is recommended to check other exons. Finally, although*BRCA1* is a critical gene playing role in several CRCs, it maybe plays an insignificant role in this type of CRC and other studies confirm this subject [22].There has not been strong evidence that colon cancer is part of the *BRCA1* phenotype. Although further studies are needed with a higher confirmation rate of colon cancers.

One of the most notable aspects of our study is that, this is the first time that the role of *BRCA1* mutations has been analyzed in this type of colorectal cancer and suggest that other *BRCA1* exons investigate.

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Competing interests

The authors declare that they have no competing interests.

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA: a cancer journal for clinicians 2011;61(2):69-90.
2. Lichtenstein P, Holm NV, Verkasalo PK, Iliadou A, Kaprio J, Koskenvuo M et al. Environmental and heritable factors in the causation of cancer—analyses of cohorts of twins from Sweden, Denmark, and Finland. New England journal of medicine 2000;343(2):78-85.
3. Kaz AM, Brentnall TA. Genetic testing for colon cancer. Nat Clin Pract Gastroenterol Hepatol 2006;3(12):670-9.
4. Sieber OM, Lipton L, Crabtree M, Heinimann K, Fidalgo P, Phillips RK et al. Multiple colorectal adenomas, classic adenomatous polyposis, and germ-line mutations in MYH. New England journal of medicine 2003;348(9):791-9.
5. Abdel-Rahman WM, Peltomaki P. Lynch syndrome and related familial colorectal cancers. Critical Reviews™ in Oncogenesis 2008;14(1)
6. Lindor NM, Rabe K, Petersen GM, Haile R, Casey G, Baron J et al. Lower cancer incidence in Amsterdam-I criteria families without mismatch repair deficiency: familial colorectal cancer type X. Jama 2005;293(16):1979-85.
7. Engel C, Loeffler M, Steinke V, Rahner N, Holinski-Feder E, Dietmaier W et al. Risks of less common cancers in proven mutation carriers with lynch syndrome. Journal of Clinical Oncology 2012;30(35):4409-15.
8. Ku C-S, Cooper DN, Wu M, Roukos DH, Pawitan Y, Soong R et al. Gene discovery in familial cancer syndromes by exome sequencing: prospects for the elucidation of familial colorectal cancer type X. Modern Pathology 2012;25(8):1055-68.
9. Caestecker KW, Van de Walle GR. The role of BRCA1 in DNA double-strand repair: past and present. Experimental cell research 2013;319(5):575-87.
10. Cavanagh H, Rogers KM. The role of BRCA1 and BRCA2 mutations in prostate, pancreatic and stomach cancers. Hereditary cancer in clinical practice 2015;13(1):1.
11. Sopik V, Phelan C, Cybulski C, Narod S. BRCA1 and BRCA2 mutations and the risk for colorectal cancer. Clinical genetics 2015;87(5):411-8.
12. Wittwer CT, Reed GH, Gundry CN, Vandersteen JG, Pryor RJ. High-resolution genotyping by amplicon melting analysis using LCGreen. Clinical chemistry 2003;49(6):853-60.
13. Taylor CF. Mutation scanning using high-resolution melting. Biochemical Society Transactions 2009;37(2):433-7.
14. Zeinalian M, Hashemzadeh-Chaleshtori M, Salehi R, Kazemi M, Emami MH. Tumor microsatellite instability and clinicopathologic features in Iranian colorectal cancer patients at risk for Lynch syndrome. Journal of research in medical sciences: the official journal of Isfahan University of Medical Sciences 2015;20(2):154.
15. Carethers JM, Stoffel EM. Lynch syndrome and Lynch syndrome mimics: The growing complex landscape of hereditary colon cancer. World journal of gastroenterology: WJG 2015;21(31):9253.
16. Wyman C, Ristic D, Kanaar R. Homologous recombination-mediated double-strand break repair. DNA repair 2004;3(8):827-33.
17. Gudmundsdottir K, Ashworth A. The roles of BRCA1 and BRCA2 and associated proteins in the maintenance of genomic stability. Oncogene 2006;25(43):5864-74.
18. Phelan C, Iqbal J, Lynch H, Lubinski J, Gronwald J, Moller P et al. Incidence of colorectal cancer in BRCA1 and BRCA2 mutation carriers: results from a follow-up study. British journal of cancer 2014;110(2):530-4.
19. Thompson D, Easton D, Consortium BCL. Variation in cancer risks, by mutation position, in BRCA2 mutation carriers. The American Journal of Human Genetics 2001;68(2):410-9.
20. Ford D, Easton D, Stratton M, Narod S, Goldgar D, Devilee P et al. Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. The American Journal of Human Genetics 1998;62(3):676-89.

21. Moynahan ME. The cancer connection: BRCA1 and BRCA2 tumor suppression in mice and humans. Oncogene 2002;21(58)
22. Ford D, Easton DF, Bishop DT, Narod SA, Goldgar DE. Risks of cancer in BRCA1-mutation carriers. The Lancet 1994;343(8899):692-5.

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Persistency of dexamethasone induced hypertension in male wistar rat model

Rat hypertension

Mohammadjavad Nazarpour Kashani[1], Abdollah Amirfarhangi[2], Vahid Khani[1], Nima Rahimi Petroudi[1], Habib Ghaznavi[3], Saeed Mehrzadi[4]
[1]School of Medicine, Iran University of Medical Science, Tehran,
[2]Cardiology Department, Rasoul Akram Hospital, Iran University of Medical Science, Tehran,
[3]Zahedan University of Medical Science, Zahedan,
[4]Department of Pharmacology, School of Medicine, Iran University of Medical Science, Tehran, Iran

Abstract

Aim: Dexamethasone (Dexa) attenuate the progression of many diseases, but despite its beneficial effects can be caused hypertension (HTN). Material and Method: According to this finding, we study the persistence of Dexa induced HTN. Experimental design includes 30 Adult male Wistar rats that divided into three groups (Dexa2, Dexa3, Control; N=10). Results: Dexa (20µg/kg/day, in a volume of 1 mL/kg) daily was injected subcutaneously for two months (Dexa2) and three months (Dexa3). Systolic blood pressure was measured periodically using the tail-cuff method with a photoelectric sensor (NIPREM 546, Cibertec S.A, Madrid, Spain) along the study. Discussion: We found that 3-month injection of Dexa induced HTN furthermore in rats, persist for two months after withdrawing of injection whereas injection for 2month has less persistency (10days).

Keywords

Dexamethasone; Hypertension; Blood Pressure; Heart Rate

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Corresponding Author: Abdollah Amirfarhangi, Cardiology Department, Rasoul Akram Hospital, Sattar khan, Tehran province, Tehran, Iran.
T.: +98 64352463 F.: +31 64352531 E-Mail: aamirfarhangi@yahoo.com

Introduction

One of the most common cardiovascular diseases is hypertension (HTN) [1] and cause main Concern for societies because of its morbidity and mortality [2]. The prevalence of HTN is significantly different around the world. A research study estimated that the prevalence of HTN in adult and elderly population of Iran were about 23% and 50%, respectively [3]. Animal models are needed for evaluation of the effect of antihypertensive drugs before using in human trials so we should induce HTN in animal models [2]. There are several types of models for inducing HTN in animals such as surgically induced HTN, endocrine HTN, dietary HTN, neurogenic HTN Chemically Induced HTN, etc. [2]. Also, for a trial of HTN complication's treatment, we need to evaluate it in animal models, and this complication is created when HTN is chronic [2]. Therefore, method induces persistent HTN is suitable in the research study. Glucocorticoids are a subtype of chemically that induced HTN [3]. Dexamethasone (Dexa) is used for the treatment of many diseases such as rheumatologic disorders, allergies, etc. [4]. In spite of its useful effects in treatment, in the long term, it causes HTN, cataracts, osteoporosis, etc. According to the mentioned, in this study we evaluated the persistence of Dexa induced HTN after withdrawing the injection of Dexain 8 & 12 weeks and the comparison of them in an experimental model.

Material and Method

Animals

In this study, adult male Wistar rats weighing 200–250 g (n = 30) were obtained from Pasteur's Institute, Tehran, Iran. Rats were housed five per cage in one colony room at the permanent temperature of 22 ± 1C (50 ± 10% humidity) on a 12-h light/dark cycle with free access to water and food. The experimental protocol for animal care and handling was according to the guidelines of the National Institute of Health guide for the care and use of Laboratory Animals (NIH Publications No. 8023, Revised 1978). The rats were randomly divided into three groups (number of each group = 10); Two groups were injected Dexa for 8 and 12 weeks (Dexa-8, Dexa-12) and the last group served as a control. Before injection of Dexa, three rats were randomly selected from each group to measure their systolic blood pressure (SBP) and heart rate (HR) with the tail-cuff method. Dexa (20μg/kg/day, in a volume of 1 mL/kg) was administered subcutaneously every day, and dosages were adjusted every week according to changes in body weight.

Systolic blood pressure and heart rate measurements

SBP were measured periodically using the tail-cuff method with a photoelectric sensor (NIPREM 546, Cibertec S.A, Madrid, Spain) along the study. During the injection and after withdrawal, measurements were taken every two weeks. For each animal, BP and PR were determined several times in every measurement and data were noted valid if there was a maximum of 10 mm Hg difference between 4 consecutive measurements.

Statistical analysis

All data were expressed as mean ± std. One way ANOVA, followed by Turkey's post hoc test, was used for each group at different time points. In all analyses, the null hypothesis was rejected at the level of >0.05.

Results

Dexa subcutaneously injected to rats and blood pressure rise significantly after 2 weeks (fig 1,2). Blood pressure was rising during injection (Fig1,2) ($p<0.001$).

In the group that received Dexa for 8 weeks, 10 days after stopping of injection, blood pressure significantly remained high in comparison to the control group ($p<0.05$). Measurement of blood pressure in the 21st day showed there isn't a significant difference between groups.

In group that Dexa was injected for 12 weeks, 2, 4 and 8 weeks after stopping injection, the deposit of decrease, blood pressure have a significant difference in comparison to the control group ($p<0.001$).

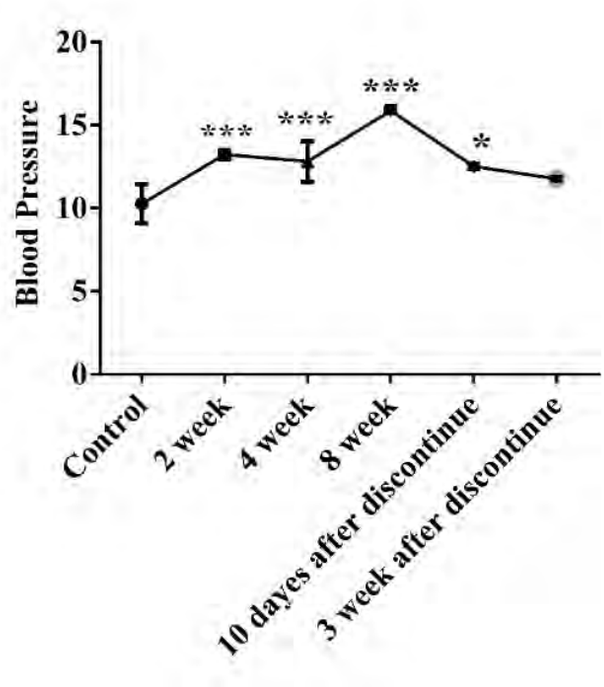

Figure1. during 8 weeks of Dexa injection and injection interrupt, blood pressure measured by tail cuff. The findings show an increase during Dexa injection.

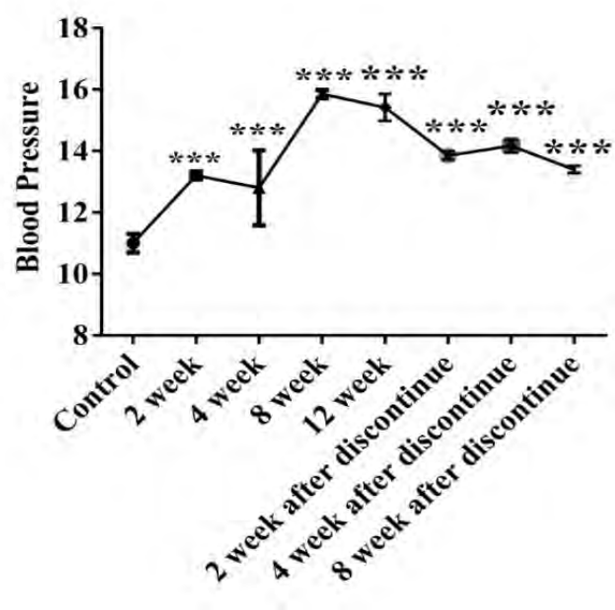

Figure 2. 12 weeks of Dexa injection and injection interrupt, blood pressure measured by tail cuff. The findings show an increase during Dexa injection. In this part of study, the blood pressure remain high much longer.

About heart rate, in Dexa-8 group, the effect of Dexa was not significant with contrast control group (fig.3). In fig.4, in spite of significant rising in heart rate after two and four weeks of injection ($p<0.05$, $p<0.001$), it was not permanent in during of injection and after discontinuation.

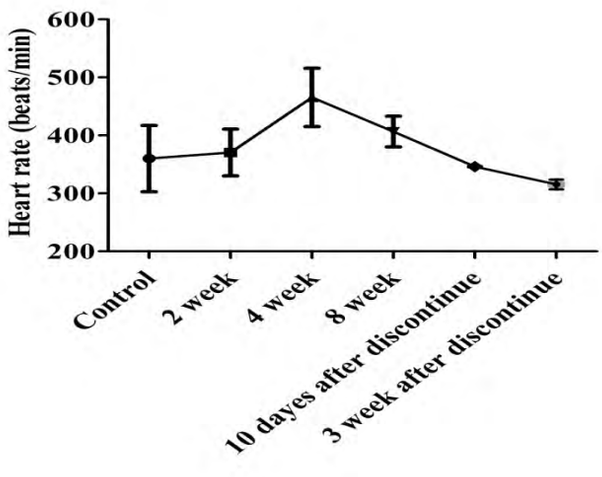

Figure 3. 8 weeks injection of Dexa and injection interrupt. Pulse rate measured by tail cuff.

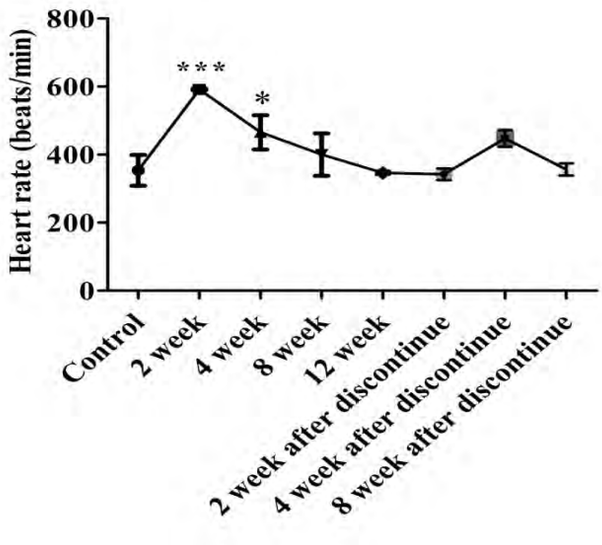

Figure 4. 12 weeks injection of Dexa and injection interrupt. Pulse rate measured by tail cuff (*P < 0.05, ***P < 0.001).

Discussion

There are several types of models for inducing HTN in animals such as surgically induced HTN, endocrine HTN, chemically Induced HTN, etc. [2]. Glucocorticoids are a subtype of chemically Induced HTN method that decreases in serum reactive nitrogen intermediate (NOx) concentration and endothelial nitric oxide synthase (eNOS), mRNA levels in heart, kidney, and liver in mice is accompanied with an injection of it [5-8]. Whiteworth et al. found that Dexa-induced hypertension is not due to its mineralocorticoid activity[9]. Although corticosteroids, especially Dexa, widely used for induction of blood pressure in animal models, there are very few studies about stability and long-term blood pressure in laboratory animals. The administration of Dexa (2.5 mg kg–1 week–1, sc) increased systolic blood pressure by 41 ± 6 mm Hg after 14 days of treatment, associated with elevations of urine volume and fluid intake and loss of body weight [9]. In a study, Dexa significantly increased SBP from 113 ± 4 to 139 ± 6 mmHg. Just administeration of N-Acetyl cysteine did not affect SBP. In the group that treated by NAC + Dexa than that of Dexa-treated rats, SBP was lower significantly [10]. Study of Lexian Hu et al. showed the administration of Dexa increased SBP (104 +/- 3 to 122 +/- 3 mm Hg) and decreased thymus and body weight [11]. In other study, SBP increased from 122 ±5 to 136±3 mm Hg due to 13 days subcutaneously administeration of Dexa [6, 11]. As can be seen, despite the common use of Dexa as a model for blood pressure induction, it is not considered that how long it remains stable? Therefore, it may be high blood pressure returns to normal again, even without any interference. This is important, because the responses of antihypertensive drug may be unrealistic. Therefore, we attempted to investigate this matter in an animal model. In our study, subcutaneously injection of Dexa for 8 & 12 weeks increased blood pressure significantly and because of its persistence is important in research studies that need chronic induced HTN, we decided to evaluate it. We found that 3-month injection of Dexa in rats furthermore that induce HTN to persist for two months after withdrawing of injection whereas injection for two months has less persistency (10days). With due attention to this result, Dexa induced HTN is suggested for studies that need inducing of chronic HTN.

Conclusion

This experimental evidence indicates Dexa subcutaneous injection for a period of 8 & 12 weeks results in a notable blood pressure rise. Furthermore, we evaluate the persistency of this well-known drug because of the importance of chronic induced HTN in researches. Therefore, we establish that Dexa injection for 3 months in rats furthermore that induce HTN to remain for two months after injection withdraw whereas two-month injection has 10days persistency. So, based on these evidence we can conclude that, the persistence of high blood pressure may be based on Dexa injection period.

Conflict of interest

The authors declare no conflict of interest related to the research covered in this article.

References

1. Tripathi K. Antihypertensive drugs, essentials of medical pharmacology. Jaypee brothers medical publishers Pvt. Ltd., New Delhi, 2003. 5: p. 503-4.
2. Sharma P, Vyawahare N, Ladhha A. Preclinical screening models for hypertension in rodents: a review. Pharmacologyonline. 2010; 3: 458-72.
3. Rezazadehkermani M. Epidemiology and heterogeneity of hypertension in Iran: a systematic review. Archives of Iranian Medicine. 2008;11(4):444-52.
4. Beard EL. The American Society of Health System Pharmacists. JONA'S healthcare law, ethics, and regulation. 2001:3(3):78-9.
5. Tonolo G. Chronic low-dose infusions of Dexamethasone in rats: effects on blood pressure, body weight, and plasma atrial natriuretic peptide. Journal of Hypertension. 1988;6(1):25-32.
6. Whitworth JA, Deanna G, John A, Bruce SA. The hypertensive effect of synthetic glucocorticoids in man: the role of sodium and volume. Journal of Hypertension. 1989:7(7):537-49.
7. Iuchi T, Akaike M, Mitsui T, Ohshima Y, Shintani Y, Azuma H, et al. Glucocorticoid excess induces superoxide production in vascular endothelial cells and elicits vascular endothelial dysfunction. Circulation Research. 2003:92(1):81-7.
8. Wallerath T, Gödecke A, Molojavyi A, Li H, Schrader J, Förstermann U, et al. Dexamethasone lacks effect on blood pressure in mice with a disrupted endothelial NO synthase gene. Nitric Oxide. 2004:10(1):36-41.

9. Nasjletti A, Erman A, Cagen LM, Baer PG. Plasma concentrations, renal excretion, and tissue release of prostaglandins in the rat with dexamethasone-induced hypertension. Endocrinology. 1984:114(3):1033-40.
10. Krug S, Zhang Y, Mori TA, Croft KD, Vickers JJ, Langton LK, et al. N-acetylcysteine prevents but does not reverse dexa-induced hypertension. Clinical and Experimental Pharmacology and Physiology. 2008:35(8):979-81.
11. Hu L, Zhang Y, Lim PS, Miao Y, Tan C, McKenzie KU, et al. Apocynin but not L-arginine prevents and reverses Dexamethasone-induced hypertension in the rat. American journal of hypertension. 2006:19(4):413-8.

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The effect of proton pump inhibitors on glycemic control in patients with type II diabetes

Hamed Mehdinezhad Gorji[1], Neda Mahdinezhad Gorji[2], Ahmad Vasel[3], Besharat Rahimi[1]
[1]Advanced Thoracic Research Centre, Tehran University of Medical Science, Tehran,
[2]Fatemeh Zahra Infertility and Reproductive Health Research Center, Babol University of Medical Sciences, Babol,
[3]Department of Pediatric Cardiology, Rajaie Cardiovascular Medical and Research Center, Iran University of Medical sciences, Tehran, Iran

Abstract

Aim: Recent studies have shown that gastrin, like other incretin hormones such as GLP1, stimulates the proliferation of pancreatic β-cells and neogenesis, which seems to be able to double insulin level while taking oral glucose. Proton pump inhibitors decrease acid levels and cause relative hypergastrinemia which can better control hyperglycemic state. The present study intended to determine the effect of proton pump inhibitors (omeprazole) on glycemic control in patients with Type II diabetes visiting the endocrinology clinic of Imam Hossein Hospital in the first half of 2013. Material and Method: The present clinical trial study (before-after) was conducted on 40 patients with qualified type II diabetes during 12 weeks. Tests of FBS, HbA1c, 2hpp BS, insulin level and c-peptide were taken from patients before the study and they used omeprazole 20 mg twice a day for 3 months. The patients were asked to visit the clinic with the aforesaid tests results after three months. Results: Following the exclusion criteria, 8 patients (%20) were excluded from the present study. After 12 weeks of treatment with omeprazole, there was a statistically significant reduction in the mean HBA1c before (8.11±0.96) and after (7.13±0.68) the treatment at %95 confidence level (P-value<0.001). Moreover, after 12 weeks of treatment with omeprazole, there was a reduction in the mean 2HPPBS and FBS before and after the treatment which was statistically insignificant in 2HPPBS and significant in FBS (respectively P-value=0.1 & P-value=0.01). Discussion: It was concluded that the treatment with omeprazole increases insulin level, decreases FBS and HbA1c and subsequently improves hyperglycemic state and can be used with other anti-hyperglycemic medications especially in diabetic patients with digestive problems. However, further research is required in this regard.

Keywords

Diabetes Mellitus; Gastrin; Hb A1c; Proton Pump Inhibitor

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Corresponding Author: Besharat Rahimi, Advanced Thoracic Research Centre, Tehran University of Medical Science, Tehran, Iran.
T.: 0098218589591 F.: 0098218589592 E-Mail: drleventalbayrak@gmail.com

Introduction

Diabetes is a chronic metabolic disorder that is highly prevalent throughout the world. Currently, about 366 million people have diabetes around the world which will be reaching 552 million by 2030 according to predictions. About %95 of these patients have type II diabetes [1]. According to statistics in 2007, diabetes was responsible for over 71,000 deaths as an underlying disease and for over 160,000 deaths as a risk factor in America [2]. Iran is no exception i.e. diabetes has become one of the principal health problems in the country in recent years. According to Iranian Diabetes Association, over 6 million people had diabetes in 2013 while over 4,500,000 Iranians had diabetes in 2012 in Iran. Over %8.7 of the country's population has diabetes. The average cost is $414 per diabetic person. Diabetes mellitus is a chronic disease with complex pathophysiology that is associated with not only insulin deficiency in type I diabetes, insulin resistance and progressive destruction of pancreatic β-cells in type II diabetes but also other pathologies such as increased lipolysis, decreased incretin hormones or incretin hormones resistance, hyperglucagonemia, increased absorption of glucose by the kidneys and brain insulin resistance [3]. Nevertheless, the type I and type II hyperglycemia is caused by the partial or complete failure of pancreatic β-cell mass [4]. Diabetes is associated with chronic vascular complications including microvascular (e.g. retinopathy, neuropathy, nephropathy) and macrovascular (e.g. coronary artery disease, peripheral vascular disease, cerebrovascular disease) complications as well as non-vascular complications such as gastrointestinal involvement, skin problems, genitourinary system disorders, cataract, glaucoma, hearing loss and infection [5]. Due to the increasing growth of this disease, the control of diabetes mellitus and its complications is the only way to deal with this problem. Research has shown that accurate glycemic control, appropriate treatment of diabetes and achieving a normal range of plasma glucose postpone the incidence and development of micro and macrovascular complications of diabetes [6 & 7]. The history of diabetes treatment and glycemic control has shown that each patient always needs more than one treatment and that effective treatment requires several medications that are used in combination to correct pathophysiological defects. The important selection criteria for medications include the effect of medications, lack of side effects, tolerability and cost-effectiveness [4]. Glycosylated hemoglobin (HbA1c) is used as a golden standard for glycemic diagnosis and assessment and as a diabetes complications severity index (8-10). HbA1c is a hemoglobin where the beta chains of hemoglobin A1 is attached to glucose with a non-enzymatic reaction; the HbA1c indicates the mean blood glucose over the last 8 to 12 weeks [11 & 12]. Gastrin is the first released incretin hormone upon the receipt of oral glucose which reinforces the glucose-dependent insulin secretion (GSIS) [13]. Acid secretion is a regular and complex process which is done by at least three types of receptors on parietal cells that are sensitive to histamine, gastrin and acetylcholine [14]. Gastrin is the main endocrine-regulating hormone in response to secretory activities upon the intake of protein food [15,16]. Proton pumps (Payment Protection Insurance: PPI) were introduced as the medicinal treatment of gastric acid-related diseases esp. gastro esophageal reflux in the late 1980s. Other uses of PPIs include the prevention and treatment of ulcers caused by NSAIDs, gastritis, gastric and duodenal ulcers, helicobacter pylori, peptic ulcers and functional dyspepsia [14,17]. Proton pump inhibitors decrease acid levels; therefore, they cause relative hypergastrinemia which can better control hyperglycemic state. Since the first medication used for PPI inhibition was omeprazole, the discussion about the safety of this medication is controversial. Research has revealed that 15 years of omeprazole intake is safe despite some side effects [18] such as hypochlorhydria that increases the risk of infections and malabsorption as well as the risk of clostridium difficile and community-acquired pneumonia in the long-term use, decreased calcium absorption which, in turn, leads to osteoporosis and increased risk of fractures. The secondary hypergastrinemia caused by PPI intake can be considered in terms of carcinoid tumor; however, the long-term intake (11 years) of omeprazole is safe [19]. With regard to the fact that few studies have been done in this area, most which were retrospective or addressed the effect of PPI on HbA1c level while did not investigate the other parameters of glucose-insulin homeostasis (FPG, Insulin Level, C-peptide, HOMA-B Cell, HOMA-IR) as well as the fact that no studies have been done in this area in Iran, the present study intended to investigate the effect of proton pump inhibitors on glycemic control in patients with Type II diabetes visiting the endocrinology clinic of Imam Hossein Hospital, with respect to geographical, racial, cultural, nutritional and lifestyle differences between Iran and other countries.

Material and Method

The present clinical trial study (before-after) was conducted on adult outpatients with type II diabetes visiting the endocrinology clinic of Imam Hossein Hospital in 2013. The patients participated in the study voluntarily in compliance with the principles of medical ethics once informed consent was obtained from all patients and they were fully informed about the process of the research. The inclusion criteria comprised type-II diabetic adults of both sexes whose diabetes had not been newly diagnosed with at least one month passed the intake of maintenance doses of oral anti-diabetic metformin or sulfonylurea or both. Moreover, patients with the previous and current intake of insulin, pioglitazone, incretin treatment, liver failure (liver enzymes level greater than 3 times the normal level), kidney disease (cr>1.5), any diabetes complications, alcohol and drug abuse, hemoglobinopathies as well as pregnant and lactating women and those taking proton pump inhibitors were excluded from the study. Like previous studies, about 40 patients were selected and entered the study once the inclusion criteria were applied. The questionnaire contained background and demographic information including age, sex, weight, height, BMI, educational level and place of residence (urban/rural) that were recorded for all patients. All patients were asked to visit the laboratory in the fasting state for venous blood sampling to measure their fasting blood glucose level, FBS, HbA1C, BUN/cr, CBC Diff, fasting insulin level and C-peptide; then, the patients underwent venous blood sampling once more within two hours later for 2hppBs (2-hour post-prandial blood sugar test). Afterwards, the patients were given

oral omeprazole 20 mg capsules twice a day and they were asked to keep on with their normal dietary and treatment during the study. Patients' compliance was assessed based on number of consumed capsules by visiting them or calling them and those whose consumed more than %80 of the capsules were considered to have compliance and their lab tests results were examined. Omeprazole was administered to patients for 3 months; they were asked to undergo FBS, HbA1c, 2hppBS, fasting insulin level and C-peptide once more after 3 months and visit the clinic with the lab tests results. Furthermore, up to one hours after the blood sampling, the plasma was separated and plasma glucose level was measured through enzymatic glucose oxidase method to prevent glycolysis. Besides, HbA1C was measured through Boronate Affinity Chromatography method using NYCOCARD kit. Fasting insulin level and c-peptide was determined via Immunoreactive assay. The indices of HOMA-β and HOMA-IR were calculated via the following formulas in the software.

$$\text{HOMA-IR} = \frac{\text{Glucose} \times \text{Insulin}}{405}$$

$$\text{HOMA-}\beta = \frac{360 \times \text{Insulin}}{\text{Glucose} - 63}\%$$

The observed raw data were entered into $SPSS_{18}$. Kolmogorov-Smirnov Test was used to evaluate the normal distribution of all data based on which appropriate statistical tests were applied. In the present study, the statistical parametric tests such as paired t-test and independent t-test were used for data analysis. Furthermore, the statistical significance level was intended less than 0.05 (P-value).

Results

About 40 patients with type II diabetes participated in the present study. Eight (%20) patients were excluded from the study following the exclusion criteria, lack of readmission and lab sampling and intake of less than %80 of omeprazole capsules. The mean duration of diabetes in participants was 5 years. Twelve (%37.5) out of the rest 32 patients (follow up) were male while 20 patients (%62.5) were female. The mean age of the participants was 54.34±10.85 years. Out of the 8 excluded patients (loss of follow), 3 were male (%37.5) and 5 were female (%62.5). The mean age of the excluded patients was 52.87±8.32 years. The results of the present study showed that there was not any statistically significant difference between the means of both groups (P-value= 0.724). Furthermore, the follow-up group was compared with the loss-of-follow group in terms of the initial values of other parameters including HbA1C, 2HppBS, FBS, BMI, Insulin and C-peptide [Table 1] indicating no statistically significant difference (P-value>0.05).

The changes in HbA1C and Insulin level of the follow-up group were measured after 12 weeks of treatment with omeprazole. The results of statistical analysis indicated a significant difference between the mean of these variables in both groups. That is, the mean HbA1c significantly decrease after 12 weeks of treatment (P-value= 0.001) while the mean insulin level significantly increased during the treatment period (P-value= 0.001) [Figure 1]. It was also indicated that the mean 2hppBS and FBS decreased after 12 weeks of treatment with omeprazole in comparison to before-treatment period, which was statistically significant only for FBS (P-value<0.05). as presented in [Table 2], there was a significant increase in C-peptide which was statistically significant (P-value>0.05).

Following 12 weeks of treatment with omeprazole, the mean β-cell function index (HOMA- β-cell) increased from 54.41±27.06 before the treatment to 79.24±45.32 after the treatment which was statistically significant (P-value=0.007). Moreover, the results showed a statistically significant difference between the mean indices of insulin resistance (HOMA-IR) before the treatment with omeprazole (5.04±2.42) and after the treatment with omeprazole (6.19±2.52) (P-value= 0.001) as displayed in [Figure 2].

Table 1. Comparison of follow-up and loss-of-follow groups

Variables	Status	N	Mean	Std. Deviation	P value
Age	Follow up	32	54.34	10.85	0.724
	Loss to follow	8	52.87	8.32	
BMI	Follow up	32	29.00	2.74	0.905
	Loss to follow	8	28.87	2.03	
HBA1c. before	Follow up	32	8.11	0.96	0.298
	Loss to follow	8	7.73	0.58	
Insulin. before	Follow up	32	13.09	5.65	0.845
	Loss to follow	8	12.64	6.30	
C-peptide. before	Follow up	32	2.94	0.98	0.548
	Loss to follow	8	2.70	1.02	
FBS. before	Follow up	32	156.03	30.87	0.817
	Loss to follow	8	153.25	26.76	
2hppBs. before	Follow up	32	241.78	64.35	0.715
	Loss to follow	8	232.75	50.34	

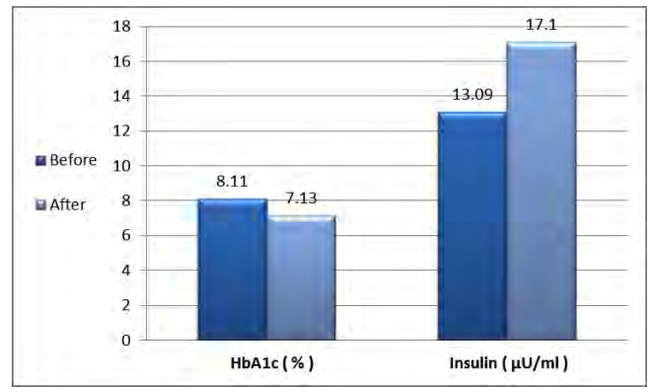

Figure 1. Changes in HbA1c and Insulin level after 12 weeks of treatments with omeprazole in the Follow-up group

Table 2. Comparison of HbA1c, FBS, 2HppBS, insulin and C-peptide before and after Omeprazole

Parameter	Before Omeprazole	After Omeprazole	P –value
HbA1c (%)	8.11±0.96	7.13±0.68	0.001
FBS(mg/dl)	156.03±30.87	146.90±23.88	0.01
2HppBs (mg/dl)	241.78±64.35	226.71±48.45	0.16
Insulin (µU/ml)	13.09±5.65	17.10±7.16	0.001
C-peptide (ng/ml)	2.94±0.98	3.40±1.30	0.003

Discussion

Many studies have investigated the effect of proton pump inhibitors on glycemic control in patients with type II diabetes. The results of the present study were in line with the findings of similar international studies. To name some, Crouch (2012) studied the electrically documented cases of type-II diabetic patients with PPI intake and without PPI intake. In his study, HbA1C level in both groups was %7.7 versus %7.1 respectively. In the present study, this value was %8.1 versus %7.1. However, the duration of PPI intake was not specified in Crouch's study (20). As mentioned earlier, many studies have been done in this area; nevertheless, none of them have measured 2HppBS, C-peptide, Insulin, FBS and indices of HOMA β-cell and HOMA-IR. As measured in the present study, the indices of HOMA β-cell and HOMA-IR qualtify β-cell function index and insulin resistance index which are calculated based on FBS and Fasting insulin via mathematical formulas. Matthews et al. (1985) studied the indices of HOMA β-cell and HOMA-IR indicating that HOMA β-cell was %100 in a young adult aged under 35 years with normal BMI while HOMA-IR index was less than 3 (normal resistance), between 3 and 5 (moderate resistance) and higher than 5 (severe resistance) [21]. In the present study, the indices of HOMA β-cell and HOMA-IR increased after 12 weeks of treatments with omeprazole in comparison to the before-treatment period which was statistically significant (P-value<0.05). In this regard, the results of the present study contradicted the findings of Singh et al.; They showed that HOMA β-cell significantly increase after pantoprazole intake while HOMA-IR remained insignificant [13]. It can be concluded that this difference contributed to racial differences, different sample size and different effects of both omeprazole and pantoprazole medications. Although this claim requires further investigations, what is certain is that insulin resistance index was higher in the diabetic patients of the present study at severe resistance level than the Indian diabetic patients in Singh's study. Nonetheless, omeprazole could meet the expectations of the present researchers to improve β-cell function due to the stimulation of gastrin secretion as an incretin hormone after omeprazole intake and its effect on stimulating β-cells, insulin secretion and β-cells proliferation. The increase of plasma gastrin level by 2 to 3 times occurs after 24 to 32 weeks of PPI intake [16]. However, the 12-week treatment with pantoprazole was associated with %50 increase in plasma gastrin level in Singh's study. This can improve hyperglycemic state with the long-term PPI intake. In this regard, the results of the present study were in line with the findings of Singh.

Bodvarsdottir studied the effect of lansoprazole with different doses on Psammomys Obesus, a kind of rats with type II diabetes, for 17 days. Measuring the morning blood glucose, gastrin and insulin level, he found that gastrin level had a 9-time increase. He also reported the significant decrease of glucose level, increase of insulin level and the %50 increase of beta cells mass. He stated that this can fortify the assumption that there is a close relationship between PPI, Gastrin and glucose-insulin homeostasis [22]. According to Suarez-Pinzon et al. [23] one of the reasons for the effect of omeprazole on the reduction of HbA1c level and improvement of glycemic state is the impact of this medication and other PPIs on delayed gastric emptying after eating a meal which leads to the timely delivery of glucose to the ileum. Appropriate environment secretes incretin hormone and reduces blood sugar level after eating a meal. Improved glycemic state can be due to the direct effect of gastrin on glucose-dependent insulinotropic peptides and GLP1 (Glucagon-Like Peptide 1) secretion from the K and L cells of small intestine; however, this has not been proved yet.

Conclusion

The strengths of the present study are that it is a prospective and randomized controlled trail (RCT) study while it is less strong than other RCT studies due to before-after trials and the absence of a placebo group. In finale, it was concluded that the treatment with omeprazole increases insulin level, decreases FBS and HbA1c and subsequently improves hyperglycemic state and can be used with other anti-hyperglycemic medications especially in diabetic patients with digestive problems. However, further research is required in this regard.

Competing interests

The authors declare that they have no competing interests.

References

1. International Diabetes Federation. Diabetes and impaired glucose tolerance: global burden: prevalence and projections aIDFWAA.
2. Association AD. Diabetes statistics: data from the 2011 national diabetes fact sheet (released Jan. 26, 2011). 2012.
3. DeFronzo RA. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. Diabetes. 2009; 58(4):773-95.
4. Boj-Carceller D. Proton pump inhibitors: impact on glucose metabolism. Endocrine. 2013; 43(1):22-32.
5. Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J. Harrison's principles of internal medicine, 19e: Mcgraw-hill; 2015.
6. Control D, Group CTR. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl j Med. 1993;1993(329):977-86.
7. Endocrinologists AAoC. American College of Endocrinology consensus statement on guidelines for glycemic control. Endocr Pract. 2002;8(Suppl 1):5-11.
8. Kilpatrick ES. Glycated haemoglobin in the year 2000. Journal of clinical pathology. 2000;53(5):335-9.
9. http://www.who.int/diabetes/publications/report-hba1c_2011.pdf.
10. Gerstein HC. Fasting versus postload glucose levels. Am Diabetes Assoc; 2001.
11. Rohlfing CL, Wiedmeyer H-M, Little RR, England JD, Tennill A, Goldstein DE. Defining the relationship between plasma glucose and HbA1c. Diabetes care. 2002;25(2):275-8.
12. McCulloch D. Estimation of blood glucose control in diabetes mellitus. Up to Date. 2006.
13. Singh PK, Hota D, Dutta P, Sachdeva N, Chakrabarti A, Srinivasan A, et al. Pantoprazole Improves Glycemic Control in Type 2 Diabetes: A Randomized, Double-Blind, Placebo-Controlled Trial. The Journal of Clinical Endocrinology & Metabolism. 2012;97(11):E2105-E8.
14. McDonagh M, Carson S, Thakurta S. Drug Class Review: Proton Pump Inhibitors: Final Report Update 5 [Елект ронний ресурс]. Portland (OR): Oregon Health & Science University. 2009.
15. Dockray G, Dimaline R, Varro A. Gastrin: old hormone, new functions. Pflügers Archiv. 2005;449(4):344-55.
16. ML. S. Gastric secretion. CurrOpinGastroenterol 2010;26:598-603.
17. Parikh N, Howden CW. The safety of drugs used in acid-related disorders and functional gastrointestinal disorders. Gastroenterology clinics of North America. 2010;39(3):529-42.
18. Rooman I, Lardon J, Bouwens L. Gastrin stimulates β-cell neogenesis and increases islet mass from transdifferentiated but not from normal exocrine pancreas tissue. Diabetes. 2002;51(3):686-90.
19. Mefford IN, Wade EU. Proton pump inhibitors as a treatment method for type II diabetes. Medical hypotheses. 2009;73(1):29-32.
20. Crouch MA, Mefford IN, Wade EU. Proton pump inhibitor therapy associated with lower glycosylated hemoglobin levels in type 2 diabetes. Journal of the American Board of Family Medicine: JABFM. 2012;25(1):50-4.
21. Matthews D, Hosker J, Rudenski A, Naylor B, Treacher D, Turner R. Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985;28(7):412-9.
22. Bodvarsdottir TB, Hove KD, Gotfredsen CF, Pridal L, Vaag A, Karlsen AE, et al. Treatment with a proton pump inhibitor improves glycaemic control in Psammomys obesus, a model of type 2 diabetes. Diabetologia. 2010;53(10):2220-3.

23. Suarez-Pinzon WL LJ, Brand SJ, Rabinovitch A. Combination therapy with epidermal growth factor and gastrin induces neogenesis of human islet {beta}-cells from pancreatic duct cells and an increase in functional {beta}-cell mass. . J Clin Endocrinol Metab. 2005;90:3401-9.

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Investigating the prevalence of HTLV and HCV infection in blood donors (for the first time) in blood transfusion organization of Kermanshah, Iran

Bahare Zalei[1], Daryoush Pourmand[2], Yousef Rahmani[3], Soraya Bilvaye[4]
[1]Imam Ali Hospital, [2]Department of Medical Laboratory Sciences, School of Paramedicine,
[3]Clinical Research Development Center, Imam Ali and Taleghani Hospital, [4]Department of İmmunology,
School of Medicine, Kermanshah University of Medical Sciences, Kermanshah, Iran

Abstract

Aim: blood transfusion is one of the most effective ways of HTLV and HCV transmission, so routine screening of blood donors is essential to reduce the risk of transmission. HCV virus is associated with liver cirrhosis, hepatocellular carcinoma, and non-Hodgkin lymphoma and HTLV virus is associated with diseases of ATL, HAM / TSP and HAU. As these viruses have high prevalence in Iraq, in the neighborhood of Kermanshah, it is essential to conduct a study on the prevalence of this virus among blood donors in Kermanshah to increase the safety of blood transfusion. Material and Method: In this study, 470 blood donors referred for the first time to blood transfusion organization were randomly selected and they were examined through ELISA screening test and Western confirmatory test for HTLV and ELISA screening test and RIBA confirmatory test for HCV virus. Demographic data were separately recorded in each individual file. Results were statistically analyzed using SPSS 16 software. Results: 90% of blood donors were male and 10% of them female. Most of them (42.1 percent) were in the age group of 20-29 years. Only one case (0.2%) had positive result by ELISA method for HTLV, but it became negative by Western blot method and one person (0.2%) had positive result by using ELISA method and RIBA confirmatory test for HCV. Discussion: according to the results of this study, it seems that the prevalence of HTLV and HCV is not high among blood donors in Kermanshah. However, due to need to prevent the transmission of infection through blood transfusion, screening the blood donors with high-risk behavior (having Tattoo, having multiple sexual partners, intravenous administration of drugs, surgery) in terms of HTLV and screening all blood donors in terms of HCV are recommended.

Keywords

Prevalence; Blood Transfusion; HTLV; HCV; Kermanshah

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Corresponding Author: Daryoush Pourmand, School of Paramedicine, Department of Medical Laboratory Sciences, Kermanshah University of Medical Sciences, Kermanshah, Iran. E-Mail: pourmand_d@yahoo.com

Introduction

Due to high viral load transmission, blood transfusion is one of the effective methods of viral infection such as HTLV and HCV [1,2]. Therefore, thalassemia and hemophilia patients receiving blood frequently are at risk of infection by these viruses [3]. Routine screening of blood donor is essential in terms of Antibody, HTLV, and HCV in endemic areas to reduce the risk of transmission [4] HCV virus has affected nearly 130 million people in the world [5] and it plays pathological role in patients with liver cirrhosis, hepatocellular carcinomas, and non-Hodgkin lymphoma (NHL) [6, 7]. Researchers in various studies have suggested that HCV infection due to lack of vaccine can have the highest rate of the prevalence compared to other viruses transmitted through blood among people with regular blood transfusions. Therefore, the most effective way to prevent its transmission is proper screening of blood donors [8, 9, 10,11]. Human T-lymphotropic virus (LTLV) has affected about 2010 million people in the world [12, 13, 14]. This deadly virus is considered a health problem in endemic regions such as Central Africa, South America and the Middle East (Japan, Iran, Turkey and Iraq) [15, 16] associated with serious diseases such as Adult T-cell Leukemia / Lymphoma (ATL), (HTLV-1 associated myelopathy / Tropical Spastic Paraparesis) HAM / TSP and HAU (HTLV-1 associated uveitis) [12, 13, 14]. In addition, it increases the risk of autoimmune diseases (such as polymyositis and acute rheumatic arthritis) and infectious diseases (tuberculosis, recurrent strongyloidiasis, Hansen's disease) [4]. Since the prevalence of HCV and HTLV in blood donors in varies in different parts of the country and no study has been conducted so far in Kermanshah [2] and its high prevalence in neighboring country of Iraq affects its prevalence in Kermanshah [3, 10, 16], conducting a study on the prevalence of HTLV and HCV among blood donors in Kermanshah is an essential to improve blood transfusions safety [2].

Material and Method

Study group

In this study lasted from February to May 2015, 470 first-time blood donors referring Blood Transfusion Organization in Kermanshah were selected randomly and after obtaining informed consent, demographic data such as age, gender, education , occupation, marital status, blood type, and results of clinical examinations were recorded in file of each person.

Sample collection:

In this study, 5 ml of venous blood were collected from each person through vacuum blood collection tubes containing citrate anticoagulant and then they were centrifuged at around 4500 rpm for 6 minutes, and the separated plasma was stored at -20 ° C.

ELISA and Western Blot Test for HTLV:

The ELISA screening test was conducted firstly with the help of INS HTLV Ab ULTRA Kit. Positive cases were duplicated by ELISA method and in the case of positive result; Western blot confirmatory test was conducted with the help of INNO-LIA HTLV I / II Score Kit to confirm positive cases of HTLV.

ELISA and RIBA Test for HCV:

The ELISA screening test was conducted firstly with the help of Enzygnost Anti-HCV 4.0 Kit. Positive cases were duplicated by ELISA method and in the case of positive result; RIBA confirmatory test was conducted with the help of INNO-LIA HCV Score Kit to confirm positive cases of HCV.

Statistical analysis:

The results were analyzed using SPSS version 16 software and the relationship between the two parameters was considered statistically significant, if sig <0.03.

Results

Demographic information (age, gender, marital status and level of education) of 470 blood donors is shown in Table 1. In the study group, 90 percent were male and 10 percent were female, and most of them (42.1 percent) were in the age group of 20-29 years. Nonparametric test showed significant difference among male and female donors in terms of education level, at the confidence level of 95% (sig = 0.026). Blood type and weight information of all 470 blood donors is shown in Table 2. Using independent T test, it was found that there is significant differences among male and female donors in terms of weight at the confidence level of 99% (sig = 0.000).

In this study, among 470 blood donors, only one person (0.2%) showed positive test in HTLV ELISA Ab screening test for in duplicate form, while it was negative in confirmatory test of Western Blot HTLV, so frequency of HTLV was zero among the study group. On addition, only one person (0.2 percent) in HCV ELISA Ab screening test in duplicate form was positive, which it was conformed in the RIBA test, so HCV frequency in the study group was 0.2% (1 person).

Discussion

According to various studies, due to lack of hemoglobin in women in Iran, 92 percent of blood donors are male. In the present study, 90% of blood donors were male [17, 18]. In this study, one of the of blood donors (0.2%) was reported positive in terms of HTLV using ELISA test, while the result was report-

Table 1.

Parameter		Frequency	Percent (%)	Total
Gender	Male	423	90	470 (100%)
	Female	47	10	
Age(year)	10-19	10	2.1	470 (100%)
	20-29	198	42.1	
	30-39	145	30.9	
	40-49	82	17.45	
	50-59	35	7.45	
Marital status	Single	156	33.2	470 (100%)
	Married	314	66.8	
Education level	Illiterate	12	2.6	470 (100%)
	Under high school	156	33.16	
	High school	157	33.4	
	Academic education	145	30.84	

Table 2.

Parameter		Frequency	Percent (%)	Total
Blood group (ABO)	A	150	31.91	470 (100%)
	B	116	24.68	
	AB	42	8.94	
	O	162	34.47	
Blood group Rh	Positive	417	88.72	470 (100%)
	Negative	53	11.28	
Weight (Kgr)	50-59	9	2	470 (100%)
	60-69	47	10	
	70-79	142	30.2	
	80-89	162	34.4	
	90-99	77	16.4	
	>100	33	7	

ed negative using Western blot test. In Nigeria, 6.5% of blood donors were reported negative in terms of HTLV using ELISA test, while they were reported negative by using Western blot test [4]. ELISA screening test might show false positive result for some acute bacterial infections, autoimmune diseases and multiple pregnancies, due to high sensitivity, low specificity, and antibody nonspecific reactions with virus antigens as result of flu vaccine, severe acute and chronic respiratory syndromes. Therefore, positives results of ELISA test should be confirmed by confirmatory test such as Western blot test, and only those cases should be reported positive that react by both ELISA and Western Blot tests [4, 3, 19]. As type 1 and type 2 antigens of virus HTLV have high similarity and cross reaction, antibodies against type 1 and type 2 of the virus are simultaneously diagnosed in ELISA and Western blot tests. Therefore, information obtained in the study indicates the prevalence of type 1 and type 2 of HTLV virus in blood donors in Kermanshah [19]. In this study, the prevalence of HTLV among 470 blood donor was zero percent, but it was reported 0.21% in Ilam in neighborhood of Kermanshah. The prevalence of HTLV in different cities of Iran is as follows: 0.31% in Western Azerbaijan, 0.01% in Bushehr, 0.11% in Alborz, 0.18% in Hormozgan, 0.04/% in South Khorasan, and 0.38% in Khorasan Razavi [17]. Northeast areas of Iran (Mashhad, Nishapur, Sabzevar) are considered endemic in terms of HTLV [20], which due to routine screening of blood donors, the prevalence of HTLV in these areas is decreasing [17]. The prevalence of this virus among blood donors in America was reported 0.004%, 0.004% in France, and 0.042% in Brazil [19]. Significant difference in the prevalence of this virus in different areas is due to the environmental, social, cultural, and behavior conditions, and the size of the study group. In addition, the prevalence of this virus depends on its prevalence in neighboring countries such as Kuwait, Iraq and Turkmenistan [21]. We believe that blood donors are healthy people in the community [16]. Thus, given the zero prevalence of HTLV in blood donors in this study, it seems that to prevent transmission of this virus and to prevent the spread of diseases associated with it, screening blood donors with high-risk behaviors (having tattoo, having multiple sexual partners, intravenous administration of drugs, surgery, needle stick, and living in prison) is necessary in Kermanshah [19].

In our study, the prevalence of HCV was 0.2%. Its prevalence was 0.037% among blood donors in Ilam [22], 0.18% in Rasht, 0.32% in Gilan, 0.12% in Golestan, 0.09% in Tehran, 0.17% in Qazvin, 0.2% in Arak, 0.2% in Shahrekord, 0.27% in Isfahan, 0.2% in Bushehr , 0.21% in Shiraz, 0.3% in Jahrom, and 0.03% in South Khorasan [23]. The prevalence of this virus among blood donors in the world varies from 0.004% to 1.96% [2], which these differences in various regions are due to the population studied, the size of the study group, study courses, geographical location, and risk factors (having Tattoo, unprotected sex, surgery, and injection of substances), methods, and test kits [23]. The rate of HCV in Iran due to routine screening of blood donors and technical progress of domestic erythropoietin that reduces the need for blood transfusions in patients decreases [24]. However, the transmission of this virus through blood transfusion is a major concern of public health [23], since control and prevention of HCV infection and determining its risk factors are very complex and due to lack of vaccines and appropriate treatment, the best way to cope with HCV is preventing its transmission. For this purpose, routine screening should be conducted in terms of HCV for all blood donors in Kermanshah [10].

Conclusion

Due to the prevalence of HTLV and HCV in blood donors in Kermanshah, HTLV screening test is recommended for blood donors with high-risk behavior and HCV screening test is recommended routinely for all blood donors. HTLV positive cases with ELISA test should be confirmed by Western blot method and to diagnose HCV, it is better that after ELISA and RIBA, RT-PCR test to be performed, because there is the possibility of false positive result in ELISA and RIBA tests. It is recommended that a study with larger to be conducted in this regard in Kermanshah.

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Competing interests

The authors declare that they have no competing interests.

References

1. 1.Emerging Infectious Threats to the Blood Supply:Seroepidemiological Studies in Iran – a Review.Gharib Karimi,Ahmad Gharehbaghian,Mohammad Fallah Tafti,Vida Vafaiyan. Transfus Med Hemother.2013;40:210–7.
2. Prevalence and Trends of Transfusion-Transmissible Viral Infections among Blood Donors in South of Iran: An Eleven-Year Retrospective Study. Fatemeh Farshadpour,Reza Taherkhani,Saeed Tajbakhsh,Marziyeh Gholizadeh Tangestani,Gholamreza Hajiani,Nasrin Sharifi,Sakineh Taherkhani,Abdolreza Nejadbolkheyr. PLOS ONE.2016;2001-18.
3. Epidemiology, Treatment, and Prevention of Human T-Cell Leukemia Virus Type 1-Associated Diseases. Clinical Microbiology Reviews. July 2010; Vol. 23,No. 3 p.577–89.
4. Seroprevalence and molecular epidemiology of HTLV-1 isolates from HIV-1 co-infected women in Feira de Santana, Bahia, Brazil. de Almeida Rego FF, Mota-Miranda A, de Souza Santos E, Galvão-Castro B, Alcantara LC. AIDS Res Hum Retroviruses. 2010;Dec;26(12):1333–9.
5. HIV, HBV and HCV Coinfection Prevalence in Iran - A Systematic Review and Meta-Analysis. Fahimeh Bagheri Amiri,Ehsan Mostafavi,Ali Mirzazadeh. PLOS ONE, March 31. 2016.
6. Hepatitis C Virus Transmission in a Pediatric Oncology Ward: Analysis of an Outbreak and Review of the Literature. Antje Knöll, Magdalena Helmig, Ove Peters, and Wolfgang Jilg. Laboratory Investigation,March 2001,Volume 81,Number 3, p. 251, 2001.
7. HCV natural history: the retrospective and prospective in perspective. Alter HJ. J Hepatol. 2005;43:550-2.

8. Epidemiology of Transfusion Transmitted Infection among Patients with β-Thalassaemia Major in Pakistan. Rizwan Ahmed Kiani,Muhammad Anwar,Usman Waheed,Muhammad Javaid Asad,Saleem Abbasi,Hasan Abbas Zaheer. Journal of Blood Transfusion Volume. 2016;5 pages.
9. Seroprevalence of Hepatitis C, Hepatitis B ,Cytomegalovirus, and Human Immunodeficiency Viruses in Multitransfused Thalassemic Children in Upper Egypt. Ramadan A. Mahmoud,Abdel-Azeem M. El-Mazary,and Ashraf Khodeary. Advances in Hematology Volume. 2016;7 pages.
10. Prevalence and trend of hepatitis C virus infection among blood donors in Iran: A systematic review and metaanalysis. Mazaher Khodabandehloo, Daem Roshani, Kourosh Sayehmiri. J Res Med Sci. 2013;18:67482.
11. Epidemiology of hepatitis C virus in Iran. Reza Taherkhani,Fatemeh Farshadpour. World J Gastroenterol. 2015 October 14; 21(38):10790-810.
12. Epidemiological Aspects and World Distribution of HTLV-1 Infection. Gessain A, Cassar O. Frontiers in microbiology. 2012;3:388.
13. Investigation of anti- HTLV I/II seroprevalence in healthy blood donors in Izmir region, Turkey .R. Sertoz, A. Turhan, H. Bozkurt et al.Mikrobiyoloji Bulteni.2010;vol.44,no.4,pp.579–84,
14. HTLV-1 Infection as a Serious Health Issue among Iranian Multi-Transfused Patients:Evidence from a Systematic Review and Meta-Analysis.Dayyani M, Hedayati-Moghaddam MR, Amini AR. IJBC. 2015;7(2): 85-94.
15. Human T-Lymphotropic Virus Type 1 Prevalence in Northeastern Iran, Sabzevar:An Epidemiologic-Based Study and Phylogenetic Analysis. Mahmoud Reza Azarpazhooh, Kazem Hasanpour, Mohsen Ghanbari, S.A. Rahim Rezaee, Baratali Mashkani, Mohammad Reza Hedayati-Moghaddam, Narges Valizadeh, Reza Farid Hosseini, Mohsen Foroghipoor, Azadeh Soltanifar, Maryam Sahebari, Keyhan Azadmanesh,Gholahossein Hassanshahi,and Houshang Rafatpanah. AIDS Research and Human Retroviruses. 2012;Volume 28, Number 9.
16. Verdonck K, Gonzalez E, Van Dooren S, Vandamme A-M, Vanham G, Gotuzzo E. Human T-lymphotropic virus 1: recent knowledge about an ancient infection. Lancet Infect Dis. 2007;7:266–81.
17. A Systematic Review for Estimation of HTLV-I Infection in the Blood Donors of Iran.Mohammad Reza Hedayati-Moghaddam.Iran J Basic Med Sci. 2013;16:196-201.
18. ntroduction to Iranian Blood Transfusion Organization and Blood Safety in Iran.H Abolghasemi, M Maghsudlu, S Amini Kafi-Abad, A Cheraghali. Iranian J Publ Health, Vol. 38, Suppl.1. 2009;pp.82-7.
19. Survey of the Seroprovalence of HTLV I /II in Hemodialysis Patients and Blood Donors in Urmia .Zakieh Rostamzadeh Khameneh, Mohammad Baradaran, Nariman Sepehrvand . Saudi J Kidney Dis Transpl.2008;19(5):838-41.
20. Epidemiology of HTLV-1 in Neyshabour, Northeast of Iran.MR Hedayati-Moghaddam, F Fathimoghadam, I Eftekharzadeh Mashhad, L Soghandi,HR Bidkhori. Iranian Red Crescent Medical Journal Iran Red Crescent Med J. 2011;13(6):424-42.
21. Global epidemiology of HTLV-I infection and associated diseases. Proietti FA, Carneiro-Proietti AB, Catalan-Soares BC, and Murphy EL. Oncogene. 2005;24:6058-68.
22. Prevalence of HIV, hepatitis B and C infections among volunteer blood donors at the blood transfusion center of Ilam city, Iran.Hasan Boustani, Enayat Anvari, Sedighe Saiadi Sartang, Mehdi Omidi, Esmaeil Rostam,Zahra Mohamadi. J Bas Res Med Sci. 2017;4(2):4-8.
23. Epidemiology of hepatitis C virus in Iran.Reza Taherkhani,Fatemeh Farshadpour. World J Gastroenterol. 2015 October 14; 21(38).
24. Control of Hepatitis C in Iran: Vision and Missions. Seyed-MMoayed Alavian. Hepatitis Monthly. 2007;7(2),57-8.

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Antimicrobial effects of harmel smoke on microbial load of hospital wards

Ali Jadidi[1], Nazanin Amini[2], Ehsanollah Ghaznavi-Rad[3,4], Gholamreza Sadrkia[1], Iman Farahani[4], Mahmood khosravi[2], Mehdi Harorani[1], Behrooz Irannejad[5], Mohammad Golitaleb[1], Mehdi Safarabadi[2]
[1]Faculty of Nursing and Midwifery, [2]School of Paramedical Sciences, [3]Molecular Research Center, Faculty of Medicine, [4]Department of microbiology and immunology, [5]MSC in Management counter bioterrorism, Emergency Medical Services & Crisis management of Markazi Province, Arak University of Medical Sciences, Arak, Iran

Abstract

Aim: Harmel (Peganum harmala L) is one of the most important herbal plants due to its antimicrobial effects. It is used traditionally for treating some diseases. This study aimed at comparing the antimicrobial effect of Harmel smoke and Nocospray solution on the microbial load of hospital wards. Material and Method: From each ward of an educational hospital, two trolleys were collected. First the samples were collected from the trolleys' surfaces and were cultured in Blood Agar and McConkey Agar culture media. Then, they were divided into two equal groups, half of them were disinfected by Harmel smoke and the other half with Nocospay solution. The results were analyzed using SPSS16. Results: The results showed that Nocospray has a stronger antibacterial effect on Staphylococcus and gram-positive bacteria, while Harmel smoke was more effective in gram-negative bacilli. Discussion: Considering that Harmel smoke has the same antimicrobial properties as Nocospray does, it is an effective agent that can be used for disinfecting medical settings.

Keywords

Harmel Smoke; Disinfection; Sterilization; Nosocomial Infection; Medicinal Herb

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Corresponding Author: Mehdi Safarabadi, Arak University of Medical Sciences, Faculty of Paramedicine, Arak, Iran.
T.: 0098215569831 F.: 0098215569832 E-Mail: M.Safarabadi14@gmail.com

Introduction

Nosocomial infection is one of the major issues that can lead to deaths in hospitalized patients. It can also exacerbate illnesses and risks of death in patients due to increased duration of hospitalization. Thus, it increases healthcare costs and has a significant impact on the economy of treatment [1]. This issue is increasingly threatening all hospitalized patients [2]. Since 1970, nosocomial infections have been responsible for more than 800,000 deaths per year. In the United States, hospitals were the eleventh leading cause of death and more than 14 percent of hospital mortalities [3]. The prevalence of nosocomial infections is directly related to the environmental hygiene of hospitals [2]. According to the studies, using contaminated instruments is the most important way of transmitting these infections [4]. According to the studies, various pathogens exist in hospital environment and equipment which are the normal flora of the skin, respiratory system, and digestive tract such as E. coli, Staphylococcus aureus, Pseudomonas, Klebsiella, and fungi. In some investigations, the number of grown colonies were higher than the average standard [5, 6]. Currently, there are disinfection methods and materials which are used in hospitals such as Ultraviolet radiation, fog-making by nebulizer, and also disinfectants such as hydrogen peroxide, glutaraldehyde, formaldehyde, ethylene oxide, Surfosept, sodium hypochlorite, and a newer brand named Nocospray [7, 8]. Although each of these substances can play a role in disinfecting the hospital wards, but environmental and human complications of using these chemical substances are inevitable [9, 10]. Therefore, using herbal ingredients has increased in recent years. The vast majority of drugs are synthetic, but at least one-third of them are produced after extraction of plants [11]. In the recent century, bacterial infections and resistance to antibiotics have been a serious threat to human health. Therefore, developing new antimicrobial compounds with minimal side effects is a critical issue. Protecting themselves against pathogens, plants have to create specific defense mechanisms and synthesize antimicrobial compounds which are always a valuable source for production of antimicrobial compounds [12].

Many of ancient drugs are still used in the same ancient forms, including medicinal smoke. Using medicinal smoke was common in more than 50 countries. It is believed that the smoke has the therapeutic effects of a drug, even stronger and faster than regular drug forms. Harmel smoke is one of these medicinal smokes [13]. Peganum harmala L., locally called Espand, is one of the most important medicinal plant species due to its antimicrobial properties and is traditionally used in the treatment of infectious diseases. Harmel contains antimicrobial substances such as Flavonoids and beta-carboline alkaloids, which are found in root, seeds, and callus of the plant. In traditional medicine of Central Asian countries (Iran, Turkey, Pakistan, Afghanistan, and Yemen), extract of different organs of harmala plant is used for different purposes such as repelling the evil eye, disinfecting the air, increasing milk secretion, excreting parasites, disposing of intestinal worms, treating rheumatism using their anti-inflammatory effect, and sexual enhancement, and also as a strong painkiller [13].

Various studies have proven the antimicrobial effect of Harmel smoke, including reduction of microbial load of Pseudomonas aeruginosa and Staphylococcus aureus in laboratory environment [1]. Reduction of Spore-forming and non-spore-forming Gram-positives, yeast, and filamentous fungi in factory farms, and also the antimicrobial effect on biofilms of Enterococcus faecalis [14, 15]. However, the antimicrobial effect of Harmel smoke in the clinical environment has not been studied. Therefore, in this study investigated the effect of Harmel smoke from Peganum harmala seeds on microbial load of the hospital environment and compared its effect with that of Nocospray, which is a common disinfectant used in burn wards and operating rooms of the hospitals.

Material and Method

The samples in this study were surfaces of the trolleys collected from different wards of an educational hospital in Arak, Iran. In this investigation, a total number of 57 trolleys were studied within two days. In the first day, 30 trolleys were collected and randomly divided into two equal groups. They were numbered and moved to two separated and isolated rooms. Before performing any disinfection, the samples were taken from the surfaces of trolleys in an area of two square centimeters, using sterile swabs moistened in sterile saline. The swabs impregnated onto trolley surfaces were treated directly on Blood Agar and MacConkey Agar culture media. Between the two groups of trolleys, one was randomly selected for disinfecting by Harmel smoke, and the other by Nocospray, which is commonly used as disinfection solution in hospitals. Nocospray disinfection process lasted one hour. A fog-making device sprayed this antiseptic solution for 30 minutes. Another 30 minutes was considered as retention time for disinfecting. In order to disinfect through Harmel smoke, 500 grams (15 grams per each cubic meter of the isolated room) of Harmel seed was purchased from a grocery and was smoked for 30 minutes by the flame. Another 30 minutes was considered to let the smoke entirely coat the trolleys' surfaces. Finally, after sampling from both groups, as performed in the first stage, the culture media were transferred to an incubator with the temperature of 37°C.

On the second day, 27 trolleys from the same wards of the educational hospital were studied. They were transferred to two separate rooms, and after numbering, the samples were collected. This time before disinfecting the trolleys by Harmel smoke and Nocospray, trolley surfaces were soaked and washed with the foam produced from a detergent. Then, they were randomly separated into two groups, 13 trolleys were collected to be disinfected by Harmel smoke and 14 by Nocospray. Disinfecting surfaces and collecting the samples were performed on the first day and the samples were cultured directly on Blood Agar and McConkey Agar culture media and transformed into an incubator with the temperature of 37°C.

After 72 hours of incubation, bacteria colonies appeared on the culture media. The colonies were counted and studied to determine the genus and species of the bacteria. Gram staining technique was performed to identify gram positivity or negativity of the bacteria. Differential tests for Gram-positive bacteria were performed including catalase test, Mannitol salt agar, and antibiogram test. Following tests were performed to identify Gram-negative bacteria: Triple Sugar Iron test, oxidative-fermentative test, and oxidase. Finally, the results were reported.

Results

In this investigation, 57 Trolleys of different hospital wards were studied, and the results are summarized in the tables and figures below.

Table 1. illustrates the growth of bacteria before disinfecting. Except in the case of Gram-negative bacilli, there is no statistically significant difference between the two methods.

Table 2. shows the growth of bacteria before disinfecting. Except in the case of Gram-negative bacilli, there is no statistically significant difference between the two methods.

Table 3. shows the growth of microorganisms after disinfecting by Harmel smoke and Nocospray, and there is no statistically significant difference between the two methods. It means that the growth of all bacteria, except Gram-positive bacilli, has been dramatically reduced.

Table 4. shows that there is no significant difference between the growth of bacteria after disinfection by Harmel smoke and Nocospray. This means that Harmel smoke has the same disinfectant property as Nocospray does.

Table 1. Comparison of positive cultures before disinfecting by Nocospray and Harmel smoke

	Number of Samples	Disinfection Method	Staphylococcus	Gram-positive Bacilli	Micrococcus	Gram-Negative Bacilli	Pseudomonas	Streptococcus
Positive culture	15	Harmel Smoke	2	15	0	9	0	0
	15	Noco-spray	5	15	1	2	0	1
Mann-Whitney test			0.2	1	0.31	0.009	1	0.31

Table 2. Comparison of positive cultures before washing and disinfecting with Harmel smoke and Nocospray

	Number of Samples	Disinfection Method	Staphylococcus	Gram-positive Bacilli	Micrococcus	Gram-Negative Bacilli	Pseudomonas	Streptococcus
Positive culture	13	Washing + Harmel smoke	12	10	6	7	1	2
	14	Washing + Nocospray	10	12	4	1	3	3
Mann-Whitney test			17/0	0.56	35/0	009/0	0.32	0.69

Table 3. Comparison of positive cultures before disinfecting by Nocospray and Harmel smoke

	Number of Samples	Disinfection Method	Staphylococcus	Gram-positive Bacilli	Micrococcus	Gram-Negative Bacilli	Pseudomonas	Streptococcus
Positive culture	15	Harmel Smoke	1	15	0	0	0	0
	15	Nocospray	3	15	0	1	0	0
Mann-Whitney test			0.29	1	1	0.31	1	1

Table 4. Comparison of positive cultures after washing and disinfecting with Harmel smoke and Nocospray

	Number of Samples	Disinfection Method	Staphylococcus	Gram-positive Bacilli	Micrococcus	Gram-Negative Bacilli	Pseudomonas	Streptococcus
Positive culture	13	Washing + Harmel smoke	7	5	2	0	0	0
	14	Washing + Nocospray	3	4	1	0	0	0
Mann-Whitney test			087/0	0.59	0.5	1	1	1

Discussion

In this study, 57 samples from different wards of an educational hospital were investigated in two stages: washing stage and no-washing stage. The results showed that before disinfection, there is no statistically significant difference in the growth rate of Gram-negative bacilli, Staphylococci, Micrococcus, Streptococcus, and Pseudomonas between the two groups of Harlem and Nocospray ($P<0.05$). However, the results show that the growth rate of gram-negative bacilli was significantly higher in Harmel smoke group ($p=0.009$). In no-washing stage, the culture results of bacteria indicate that neither Harlem group nor Nocospray group is effective on gram-positive and gram-negative bacteria. Although Harlem smoke seems to be more effective on gram-negative bacteria, this difference was not statistically significant. At this stage, the growth rate of Pseudomonas, Streptococcus, and Micrococcus was poor, but in washing stage, both methods of disinfection via Harmel smoke and Nocospray are effective on staphylococcal, gram-positive and Micrococcus. In this regard, although Nocospray seems to be more effective than Harmel smoke, but the difference was not statistically significant. Also in this stage, both methods had antimicrobial effects on gram-negative bacilli as no growth was detected on culture media after incubation. There is no similar study investigating Harlem smoke effects in clinical settings. In their study, Parvin et al. (2010) compared the effects of Harmel and Dung smoke and that of straw smoke via disk diffusion test method. Their results showed that Harmel smoke had antimicrobial effects on Staphylococcus aureus, and the diameter of the of inhibition zone increased with an increase in smoking process [1]. Parvin et al. found that Harmel smoke had antimicrobial effect on Gram-positive bacteria with or without spores, yeast, and filamentous fungi, but it was partially effective for gram-negative bacteria at high doses (8 hours of smoking); while the present study showed that Harmel smoke is more effective on Gram-negative bacilli [15]. The researchers suggest that Harmel smoke can be used as a kind of indoor disinfectant agent [15]. Most studies have focused on Harmel seed extract, for instance, the study of Mazandarani et al. (2009) showed that Bacillus licheniformis bacteria has the most sensitivity to Harmel extract, but Staphylococcus aureus, Staphylococcus epidermisis, Micrococcus loteus, Salmonella typhimorium, and Shigelladysentria, each has the sensitivity of 50 percent. Although Gram-positive bacteria were more sensitive than Gram-Negative bacteria, the difference was not statistically significant [13]. The results of the study showed that Harmel smoke can be as effective as the commercial Nocospray solutions, used as

a common disinfectant in the operation rooms and bath burn units via fog-making instruments. The Mann-Whitney test results show there is no difference between the two methods of disinfection, Harmel smoke, and Nocospray, on Staphylococcus, Gram-positive and Gram-negative bacteria ($P<0.05$). Comparing the two methods of disinfection before and after washing with detergent, there was a significant difference in the growth rate of Gram-negative bacilli. Hence, rinsing the equipment with detergents before disinfection increases the effectiveness of disinfecting.

Conclusion

The results of the present study showed that antimicrobial effect of Harmel smoke is the same as that of the commercial Nocospray solution. However, rinsing the equipment increases the disinfection effect in both methods. So, using Harmel smoke is recommended as a disinfectant in the absence of any contact with the patient and its attendant. Using this method certainly costs less and is more environmentally friendly than other kinds of chemical substances. Further research in this area is recommended.

References

1. Parvin N, Validi M, Banitalebi M, Mobini GhR, Ashrafi K, Farrokhi E, et al. Effect of medicinal smokes on some nosocomial infection factors. The journal of shahrekord university of Medical Sciences. 2010; 12(2): 71-6.
2. Amini M, Sanjary L, Vasei M, Alavi S. Frequency evaluation of the nosocomial infections and related factors in mostafa khomeini hospital "ICU" based on " nni " system. Journal of Annals of Military and Health Sciences Research. 2009;1(7):9-14.
3. Naderinasab M, Shahfarhat A, Tajzadeh P, Sorosh S, Amiri M, Vahedian M. Study of bacterial agents in nosocomial infections and infections acquired using blood culture results. daneshvarmed. 2006;(65):69-71.
4. Nobahar M, Vafaei AA. Contamination of medical devices as one of the means of transmission of nosocomial infections in hospitals of Semnan. Infectious Diseases. 2003;8(23):25-8.
5. Naddafi K, Rezaei S, Nabizadeh R, Yonesian M, Jabbari H. Density of airborne bacteria in a childrenís hospital in Tehran. J Health Environ. 2009;1(2):75-80.
6. Besharati R, Sadeghian A, Mamori G, Lashkardoost H, Sepideh gholami. Sources of bacteria causing nosocomial infections At NICU of Ghaem Hospital in Mashhad. Journal of North Khorasan University of Medical Sciences. 2013;5(1):25-9.
7. Ehrampoush MH, Davoudi M, Absalan A, Falahzadeh H. The effect of hydrogen peroxide and silver ions (h2o2+ag+) on disinfecting a steel surface infected by some pathogenic bacteria. The Journal of Toloo-e-behdasht 2009;8(26):11-5.
8. Alinajad F, Barati M. Effects of sodium hypochlorite disinfection of surfaces. Iranian Journal of Infectious Diseases and Tropical Medicine. 2002;19(7):73-8.
9. Barbut F, Menuet D, Verachten M, Girou E. Comparison of the efficacy of a hydrogen peroxide drymist disinfection system and sodium hypochlorite solution for eradication of Clostridium difficile spores. Infectcontrol hosp epidemiol. 2009;(30):507–14.
10. Grare M, Dailloux M, Simon I, Dimajo P, Laurain C. Efficacy of dry mist of hydrogen peroxide (dmhp) against mycobacterium tuberculosis and use of dmhp for routine decontamination of biosafety level 3 laboratories. Journal of clinical microbiology. 2008; (9)46:2955–8.
11. Shirazi MH, Fazeli MR, Sultan Dallal MM, Eshraghi S, Jamalifar H, Alamulhoda E. A comparative study on the antimicrobial effect of some medicinal herbal extracts and selective antibiotics against the clinical isolates of Helicobacter Pylori. J Med Plants. 2003;2(7):53-60.
12. Mazandarani M, Ghaemi EA, Ghaffari F. Antibacterial survey of different extracts of Peganum harmala L. different parts in Northeast of Golestan province (Inche Borun). Journal on Plant Science Researches. 2009;3(15):27-38.
13. Mohagheghzadeh A, Faridi P, Shams AM, Ghasemi Y. Medicinal smokes. J Ethnopharmacol. 2006;(108): 161-84.
14. Tabrizizadeh M, Zandi H, Mosaddegh MMH, Mahmodizadeh H. Comparing the antibacterial effect of peganum harmala extract and 5/25% sodium hypochlorite on enterococcus faeclis biofilm. J Shahid Sadoughi Univ Med Sci. 2014;22(3):1256-64.
15. Najafi YF, Jafari Sayadi A, Peganum hermla antimicrobial effects of smoke from its seeds can be used in industrial halls livestock. Agricultural Knowledge. 2001;11(4):83-94.
16. Shahverdi AR, Ostad SN, Khodaee S, Bitarafan L, Monsef-Esfahani HR, Jamalifar H, et al. Antimicrobial and cytotoxicity potential of Peganum harmala smoke. Pharmacognosy Magazine. 2008;4(15):236-40.
17. Http://www.alphadent.ir/product/335. Available at: 2015/8/4.
18. Shahverdi AR, Monsef EHR, Nickavar B, Bitarafan L, Khodaee S, Khoshakhlagh N. Antimicrobial activity and main chemical composition of two smoke condensates from Peganum harmala seeds. Zeitschrift für Naturforschung C. 2005;(60):9-10,707-10.

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Effect of kinesio taping in management of postural scoliosis: A randomized controlled study

Amany Mahmoud Helmy[1], Ghada Mohamed Kourah[1], Hamada Ahmed Hamada[1], Amira Hussein Draz[1], Mohamed Goda Montaser[2]
[1]Department of Biomechanics, Faculty of Physical Therapy, Cairo University, Giza,
[2]Department of Orthopedics, Faculty of Medicine Banha University, Egypt

Abstract

Aim: Postural scoliosis is a common problem which affects the population especially female subjects. Back pain tends to show the common symptom in scoliotic patients in addition to other functional problems. Purpose of this study aims to investigate the additional effect of Kinesio taping in management postural scoliosis. Material and Method: Thirty patients with postural scoliosis were randomly assigned into two equal groups A and B. Both groups received a traditional physical therapy program. While group A additionally received Kinesio taping. Baseline and post-treatment assessment for the pain severity, pressure pain threshold (PPT) of iliocostalisthoracies and iliocostalislumborum, Cobb's angle, functional disability and back range of motion were measured. Results: Mixed design MANOVA revealed significant improvement in pain and pressure pain threshold of iliocostalisthoracies and iliocostalislumborum of group A than group B ($P < 0.05$). There were significant improvements in pain, pressure pain threshold of iliocostalisthoracies and iliocostalislumborum, functional disability, and back range of motion in both groups ($P<0.05$). While there were no significant differences of the Cobb's angle in both groups or between groups after treatment. Conclusion: adding Kinesio taping to traditional physical therapy program yields improvement in pain, pressure pain threshold of iliocostalisthoracies and iliocostalislumborum on patients with postural scoliosis than traditional physical therapy alone.

Keywords

Kinesio Taping; Postural Scoliosis; Cobb's Angle

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Corresponding Author: Hamada Ahmed Hamada, Department of Biomechanics, Faculty of Physical Therapy, Cairo University, Egypt.
T.: +201117893697 E-Mail: Hamada.ahmed@pt.cu.edu.eg

Introduction

Scoliosis is defined as a lateral deviation of the spine from the normal plumb line. Commonly, there is a rotational component and deviation also in the sagittal plane (kyphosis or hyperlordosis) [1]. When scoliosis presents in adults, it is often painful causing emotional problems related to visually impaired esthetics, pain, as well as pulmonary mechanic-related problems [2].

Scoliosis is the most common type of spinal deformity, which occurs approximately 2% to 3% in children ages 10 to 16 years, girls being more at risk for severe progression by a ratio of 3.6 to 1 [3].Traditionally, scoliosis is considered as a painless condition, but in other studies there was a higher incidence of back pain in scoliosis patients and based on questionnaires, small-scale postural scoliosis may create difficulties for carrying out physical activities, so exercise capacity can be reduced, due to decreased mobility of the chest wall and produce functional disabilities [4, 5].

Postural stresses such as in scoliosis are a form of mechanical muscle stress that has been considered to be a cause of myofascial trigger points (MTP) formation and activation. [6]. The common muscles can be affected by a trigger point in scoliosis are the quadratus lumborum and the iliocostalisthoracies, iliocostalislumborum [6,7].

Kinesio Taping (KT) is an elastic tape that can be stretched to 140% of its original length, thereby exerting a constant shearing force on the skin, KT is conceived to be a therapeutic way with the following effects on the musculoskeletal system. It corrects muscle function by stimulation week muscles, reduces pain through neurological suppression, improves blood and lymph circulation; it corrects misaligned joints by retrieving muscle spasm and can contract back to the normal resting position [8].

Taping has been reported to reduce sports injury, osteoarthritis, myofascial pain syndrome, and patellofemoral pain syndrome, as well as pain, swelling and muscle spasms of patients with nervous system disorders, while increasing the range of motion and improving function; It is also; effective in correcting walking pattern and functionality [9].

Kinesio tape, an alternative taping technique, has been used to improve a variety of physiological problems, including the range of motion, based on the functions of the tape and thus has been used to be an effective treatment to restore muscle function and decrease pain [10, 11,9]. Various treatments have been proposed for scoliosis, including surgery, traction, bracing, casting, electrical stimulation, and physical therapy [12]. However, there is lack of studies assessing the effectiveness of adding Kinesio taping in management postural scoliosis, and therefore more studies are needed. The purpose of the study was to investigate the additional effect of Kinesio taping in management postural scoliosis.

Material and Method

The study was designed as a prospective, randomized controlled trial (RCT). In total, 35 patients with postural scoliosis, referred by the same orthopedic surgeons to out-clinic of the faculty of physical therapy, Cairo University, were enrolled and assessed for their eligibility to participate in the study. Their age ranged from 15 to 30 years. Thirty patients with postural scoliosis were randomly assigned into two equal group, by using a shuffled deck of cards (e.g., No. single – group A, No. double – group B). The patients were assigned randomly into two equal groups, group A; received Kinesio taping and therapeutic exercises, Group B; received therapeutic exercises and sham Kinesio taping. No subjects dropped out of the study after randomization. Written informed consent was obtained from all subjects before the baseline evaluation. Ethical approval was obtained from the institutional review board at Faculty of physical therapy, Cairo University before study commencement. The study has followed the Guidelines of Declaration of Helsinki on conduction of human research.

The inclusion criteria were patients who had postural scoliosis, caused by a symmetric muscle weakness (Cobb's angle ranged between (15-30°) at thoracic curve taken after performing Adam forward bending test, a history of back pain for more than 3 months caused by scoliosis and scoliosis with iliocostalisthoricis and iliocostalislumborum muscles affected by trigger points. Patients were excluded if they had a history of previous back surgery, structural idiopathic scoliosis, leg length discrepancy, and other disorders in the vertebral column (prolapsed disc, fracture), a systemic or local regional infection, malignity, neurodermatitis, skin diseases such as eczema or psoriasis, decompensated heart failure; were pregnant; had advanced asthma, epilepsy, intervertebral disc disease, previous surgery (spinal fusion), spinal cord anomalies and tumors, any pathological spinal anomalies, such as spondylolysis, spondylolisthesis and lumbosacral transitional anomalies that could be associated with back pain. All of the evaluation and training procedures were explained before the beginning of the study.

Patients were assessed before, and after the treatment sessions by VAS, Pressure Pain Threshold (PPT) of iliocostalisthoracies and iliocostalislumborum, Oswestery disability questionnaire for functional disability were used based on the work of Fairbank and Pynsent [13]. Schober flexion and extension techniques and lateral flexion from standing position for the range of motion of back right and left side bending [14]. Cobb's angle was measured from standing position (loaded x-ray) [1].

Both groups received traditional physical therapy exercise program, 3 sessions/week for 6 successive weeks. The group B received the same treatment intervention as the group A, with sham Kinesio taping (KT without tension). The same experienced physical therapist carried out the treatment program for both groups (10 years' experience).

Kinesio Taping: Application of a mechanical correction technique, to provide stimuli in which the body will adjust to increase tension in the skin. For the posterior superior region, begin by placing the base of the Kinesio Y strip (approximately 6-8 inches) two inches below the area to be treated, with no tension. With one hand, hold the base to ensure no tension was added. The patient moved into back flexion with rotation in the opposite direction of the desired correction, apply light to moderate, tension (25-50% of available) to the tails of the Kinesio Y strip, the "recoil" action of the tails will provide the stimulus to the skin.

Application of a fascia correction technique to provide a deeper stimulus to reduce tension within the layers of the tissue, with tension on the base. Begin with a Kinesio Y strip of approx-

imately 6-8 inches. Place the base medial to the area to be treated, with no tension. With one hand, hold the base to ensure no tension is added, have the patient move into back flexion with rotation in the opposite direction of the desired correction. Apply light tension (25% of available) to the tails of the Kinesio Y strip, with an oscillating motion. Move the band on the base along the Kinesio Y strip and initiate adherence to the skin. In both techniques, the authors initiate glue activation before any further patient movement [11]. For the posterior lower region, the technique applications were repeated, except the motions was reversed to provide stimulus in an opposite direction. The desired effect is to "unwind" the spine**.** The Kinesio Taping was applied and changed every five days [11].

Exercise program: It consisted of stretching and strengthening exercises program three sessions per week for successive six weeks [15].

Stretching exercises: The main aim of these exercises was to shift the apex of the curve to the midline and passively over correct the curve for 30 seconds stretching, 3 repetitions, 3 sets. This was through three positions.1- Patient prone: with stabilization at the iliac crest on the side of the concavity. The patient was asked to reach toward the knee with the arm on the convex side of the curve while stretching the opposite arm up and overhead. 2- Patient kneel-sitting (to stabilize the lumbar curve): patient leaned forward, so the abdomen rests on the anterior thighs stabilize the patient at the iliac crest, arms are stretched overhead bilaterally finally the patient laterally bent the trunk away from the concavity. 3- Patient side-lying on the convex side: From two positions, first the patient was in side-lying with a rolled towel at the apex of the convexity; the lumbar spine is stabilized. The second was side-lying over the edge of a mat table to stretch tight structures of a right thoracic scoliosis with stabilization of the pelvis.

Strengthening Exercises for back and trunk musculature on the convex side of the curve: The patient performed the following steps in the same order owing to progress the difficulty. 1); Patient side-lying on the concave side of the curve with stabilization at the iliac crest with a lower arm across the chest, have the patient de-rotate the trunk, lifts up the head and shoulders (lateral trunk bending), and slide the top arm down to the knee. 2); Patient side-lying: progress the difficulty of the above-mentioned exercise by having the patient clasp hands behind the head and then laterally flex the trunk against gravity. 3); Patient crock lying: Anterior pelvic tilt with the press against the mat table with shoulder and buttock. 4); from prone position: Raise head, shoulder, and both lower limbs upward. The exercise was lasting for 6 to 10 second for 10 repetitions.

Statistical analysis

All statistical measures were performed through the Statistical Package for Social Studies (SPSS) version 22 for windows. Before final analysis, data were screened for normality assumption and presence of extreme scores. This exploration was done as a pre-requisite for parametric calculation of the analysis of difference and analysis of relationship measures. To determine the similarity between the groups at baseline, subject age, height, and body weight were compared using independent t-tests.

The current test involved two independent variables. The first one was the (tested group); between subjects factor which had two levels (Group A receiving Kinesio taping with traditional physical therapy program & Group B receiving sham Kinesio taping with traditional physical therapy program). The second one was the (training periods); the within-subject factor which had two levels (pre and post). In addition, this test involved nine tested dependent variables (VAS, PPT for iliocostalisthoricise and iliocostalislamborum, Cobb's angle, Oswestry and ROM of flexion, extension, right bending, and left bending). Accordingly, 2×2 Mixed design MANOVA was used to compare the tested variables of interest at different tested groups and training periods. The MANOVAs were conducted with the initial alpha level set at 0.05.

Results

Baseline and demographic data: As indicated by the independent t-test, there were no statistically significant differences (P>0.05) between subjects in both groups concerning age, weight, and height (Table 1).

Table 1. Demographic characteristics of both groups:

	Group A	Group B	Comparison	
	Mean ± SD	Mean ± SD	t-value	P-value
Age (years)	29.33±6.94	29.06±6.01	0.112	0.911
Height (cm)	165.8±7.43	165.6±8.21	0.54	0.593
Weight (kg)	70.4±8.8	68.66±8.76	0.07	0.945

Statistical analysis using mixed design MANOVA analyzed thirty patients assigned into two equal groups. It revealed that there were significant within-subject (F = 127.999, p = 0.000) and treatment*time (F= 9.222, p = 0.000) but there were no significant effects between subject (F = 2.359, p = 0.053). Table (2) present descriptive statistic and multiple pairwise comparison tests (Post hoc tests) for theVAS, PPT for iliocostalisthoricise and iliocostalislamborum, Cobb's angle. In the same context, the multiple pair wise comparison tests revealed that there were significant decreases (p <0.05) in VAS in the post-treatment condition compared with the pre-treatment one in both groups. However, there were significant increases (p <0.05) in PPT for (iliocostalisthoricise and iliocostalislamborum) in the post-test condition compared with the pre-test one in both groups. There was no significant difference in Cobb's angle between pre and post-treatment for both groups.

Regarding between-subject effects multiple pairwise comparisons revealed that there were significant decreases (p < 0.05) in VAS, with significant increase (p < 0.05) in PPT for (iliocostalisthoricise and iliocostalislamborum) in group A compared with group B, with no significant differences in Cobb's angle between both groups (p > 0.05). While Table (3) present descriptive statistic and multiple pairwise comparison tests (Post hoc tests) for the Oswestry and ROM of flexion, extension, right bending, and left bending for both groups at different measuring periods. In the same context, the multiple pair wise comparison tests revealed that there were significant decreases (p <0.05) in Oswestry and ROM of right bending and left bending in the post-treatment condition compared with the pre-treatment one in both groups. However, there were significant increases

Table 2. Descriptive statistics and multiple pairwise comparison tests (Post hoc tests) for the VAS, PPT for iliocostalisthoricise and iliocostalislamborum, Cobb's angle for both groups at different measuring periods.

	Group A		Group B	
Variables	Pre	Post	Pre	Post
VAS	7.4 (1.88)	1.86 (0.74)	7 (1.55)	2.6 (1.05)
PPT for (iliocostalisthoricise)	1.62 (0.77)	3.26 (1.01)	1.42 (0.64)	2.07 (0.67)
PPT for (iliocostalislamborum	1.68 (0.67)	3.33 (0.88)	1.38 (0.49)	2.04 (0.46)
Cobb's angle	22.2 (3.44)	22.5 (3.4)	23.33 (3.75)	23.33 (3.75)

Within groups (Pre Vs. post)				
p-value	VAS	PPT for (iliocostalisthoricise)	PPT for (iliocostalislamborum)	Cobb's angle
Group A	0.000*	0.000*	0.000*	0.168
Group B	0.000*	0.000*	0.00*	0.999
Between groups (group A Vs. group B)				
p-value	VAS	PPT for (iliocostalisthoricise)	PPT for (iliocostalislamborum)	Cobb's angle
Pre treatment	0.531	0.433	0.166	0.396
Post treatment	0.036*	0.001*	0.0001*	0.549

VAS: Visual Analogue Scale, PPT: Pressure Pain Threshold.
*The mean difference is significant at the alpha level (p< 0.05).

Table 3. Descriptive statistic and multiple pairwise comparison tests (Post hoc tests) for the Oswestry and ROM of flexion, extension, right bending, and left bending for both groups at different measuring periods.

	Group A		Group B	
Variables	Pre	Post	Pre	Post
Oswestry	35, 6(14, 21)	15, 93(5,83)	28, 33(12,23)	14, 93(4.26)
ROM of trunk flexion	8, 73(1, 79)	10, 68(1,68)	9,6(1,45)	11,(1,45)
ROM of trunk extension	4.93 (1.16)	6.86 (1.24)	5.46 (0.99)	6.8 (0.94)
ROM of right bending	42.13 (2.89)	39.53 (2.41)	42.26 (2.91)	41.06 (2.76)
ROM of left bending	42.06 (2.49)	40.13 (2.35)	42.33 (3.03)	41.6 (2.92)

Within groups (Pre Vs. post)					
p-value	Oswestry	ROM of trunk flexion	ROM of trunk extension	ROM of right bending	ROM of left bending
Group A	0.0001*	0.0001*	0.0001*	0.0001*	0.0001*
Group B	0.0001*	0.0001*	0.0001*	0.0001*	0.0001*
Between groups (group A Vs. group B)					
p-value	Oswestry	ROM of trunk flexion	ROM of trunk extension	ROM of right bending	ROM of left bending
Pre treatment	0.145	0.157	0.187	0.901	0.795
Post treatment	0.596	0.374	0.87	0.117	0.141

*The mean difference is significant at the alpha level (p< 0.05)

(p <0.05) in ROM of flexion and extension in the post-test condition compared with the pre-test one in both groups. Regarding between-subject effects, multiple pairwise comparisons revealed that there were significant no significant differences in Oswestry and ROM of flexion, extension, right bending, and left bending between both groups (p > 0.05).

Discussion

This study demonstrated the additional effect of Kinesio taping in the management of postural scoliosis. The results showed an obvious pain reduction, increase PPT for iliocostalisthoricise and iliocostalislamborum, improve in functional disability, and back range of motion with no change in Cobb's angle after six weeks of treatment for both groups. However, the group A that receiving Kinesio taping in addition to traditional physiotherapy program had higher improvement in pain and PPT for iliocostalisthoricise and iliocostalislamborum compared with the group B that receiving traditional physiotherapy program.

These results come in agreement with Castro-Sanchez et al. [16] as they stated that people with back pain who received Kinesio taping had achieved a significantly greater reduction in disability and improvement of functional endurance of the trunk muscles. The results also come in agreement with Kase and Garcia [10,11] who stated that Kinesio taping produce a convolution area which may increase the flow of blood and lymphatic fluids due to a lifting effect, which creates a wider space between the skin and the muscle and interstitial space. The possible increase in blood circulation is theorized to affect muscle functions and improve functional disabilities [17].

In addition, the decrease in pain level may be explained through the study done by Paolini et al. [8]and Deleo[18] who said that the cutaneous stretch stimulation provided by Kinesio taping may interfere with the transmission of mechanical and painful stimuli, delivering afferent stimuli that facilitate pain inhibitory mechanisms (gate control theory) and pain reduction. Pain relief was also confirmed by research done by Gonz´alez-Iglesias et al., [19] who achieve pain-relief effects of KT applications in patients with acute whiplash injury. Research results confirm the positive influence of KT on the decrease in pain perception resulting in a lower intake of painkilling tablets. [20]

Studies of the therapeutic value of Kinesio tape have yielded evidence of significant improvements in range of motion and reduction of pain. A case reported by Garcia-M et al. [21] addressed the use Kinesio tape for treatment of myofascial trigger point pain in the shoulder. The authors reported that Kinesio tape contributed to the resolution of the patient's symptoms within a few days. Significant improvements in shoulder range of motion were observed after two days of treatment.

About back range of motion, there was marked increase of back (flexion, extension, right side bending and left side bending after treatment of patients by application of Kinesio tape and exercises there was an improvement of the range of motion, which was confirmed by some studies which have found that Kinesio tape, an alternative taping technique, has been theorized to improve a variety of physiological problems, including the range of motion, based on the functions of the tape [10, 11, 22, 9, 17, 12].

The increase in the active range of motion of back could be explained by two theories which may aid in understanding this finding. One theory is that Kinesio taping increases blood circulation in the taped area [17], and this physiological change may affect the muscle and myofascial functions after the application of Kinesio tape. An additional theory is that Kinesio tape stimulates cutaneous mechanoreceptors at the taped area, and this stimulation may affect the ROM.

In spite of the marked effect of adding Kinesio tape to the traditional exercise program there was an effect of these exercises in the improvement of functional disabilities and back range of motion in addition of relieving pain in group B which could be explained through the following;

Physical exercises prevent or reduce functional disabilities of the scoliotic patients this could explain the marked decrease of functional disability post-treatment of the traditional program in both groups. This is confirmed by work done by Rainville et al. [26] who said that the most obvious benefit of exercise is its ability to improve and maintain musculoskeletal and cardiovascular function, exercise may be useful for improving back function for patients with mechanical low back pain.

Both flexion and extension exercises programs were found to be effective in reducing functional disability in chronic mechanical low back pain patients supporting the finding of Hansen et al. [27]. Low back pain can produce reflex muscle inhibition for paraspinal muscles to prevent movement and protect the structures so, strengthening of these muscles reduces pain and improve function, as reported by Rissanen et al.[28] who found that impairment of trunk strength, flexibility and endurance are present in many people with back pain, these impairment results in part from long-term inhibition of movement and physical inactivity that results in neurological and physiological changes in the spine. These changes include weakness of the paraspinal musculature with selective loss of type tow muscle fibers, shortening of muscles and connective tissue of the spinal region.

The marked increase of these ranges could be explained via the work done by Rainville et al. [26] who found that stretching exercises can be used to eliminate impaired flexibility and restore normal trunk range of motion. In order to be successful, stretching must be performed at the patient's physiological end range and therefore within the range of motion that may induce back discomfort. Useful motions to assess include back flexion, extension, and side bending. Three sessions of stretching per week improve flexibility, but even greater gains in flexibility are made with five times per week. After flexibility had been increased, one session of stretching per week is enough to maintain the increases.

Cobb [25] asserted that physical exercises are beneficial when practiced in order to improve the muscle strength, tone, vital capacity, the range of motion and posture of the scoliotic subject. Knowledge emerging from scientific research data according to the review of literature which confirms the validity of these assertions. Multiple studies have documented the efficacy of stretching for improving trunk flexibility deficits and range of motion in patients with chronic back pain, with the average improvement of about 20% noted. Long-term compliance with a therapeutic stretching has been documented and is generally high [29, 30, 28].

Strengthening exercises were more effective in improving back muscle strength, pain relief, functional ability, physical improvement, and range of motion in patients with chronic mechanical low back pain through the evaluation of many previous randomized control trial studies [33]. Moffett et al. [33] demonstrated significantly fewer sick days at one year follow- up for subject with low back pain randomized to an exercise program that included strengthening and stretching exercises as compared with traditional general practitioner management. Taimela et al. [34] found that exercises decrease back pain and the recurrences of persistent pain occurred significantly less frequently among those who had maintained regular exercise habits after the treatment than those who had been physically inactive. On the contrary Bendix et al. [35] found that exercises had no effect on reducing back pain after performing a study and concluded that low - intensity exercise may have less effect on back pain. And this has been supported by Hansen et al. [36] who noted that no post-treatment differences in back pain after performing the exercise.

Concerning the Cobb's angle in both groups (experimental A, control B), there was no improvement recorded between pre and post-assessment. This result comes in agreement with Weinstein et al. [37], who stated that no definite evidence has shown that physical therapy or bracing reduces the risk of curve progression, corrects the existing deformity, or decrease the need for surgery. Ferraro et al. [38] concluded that exercise therapy performed for 30 minutes/day for a mean period of 2years as compared with exercise therapy performed for just 10 minutes daily, for mild scoliotic patients slowed or even halted the progression of both the curves and the humps. But in such mild functional scoliosis, one can't rule out the possibilities that specific systematic exercises would gradually correct the curve in its postural component.

On the contrary, Scheier[39]who have suggested that it is even possible that the improved biomechanics of the spine secondary to exercise therapy might have a corrective effect on the growth. Lenssincket al. [40] published a systematic review of all conservative interventions in the treatment of adolescent idiopathic scoliosis and concluded that the effectiveness of exercise therapy in reducing the curve progression is not yet established but might be promising. Simon and Harchad [41] perform a literature review for assessing exercise therapy in adolescent idiopathic scoliosis and found that many studies reported "significant" changes in the Cobb angle after treatment, which were actually of small magnitude and did not take into account the reported inter or intra-observer error rate. These studies had poor statistical analysis and did not report whether the small improvements noted were maintained in the long term.

There are some limitations of this study. First, the lack of a strictly recorded, dose-specific home-exercise program maintained during treatment. Secondly, the effect of the rehabilitation program on the participants' psychological parameters such as quality of life was not examined. In conclusion, this study shows that an additional Kinesio taping to traditional physical therapy program yields improvement in pain, pressure pain threshold of iliocostalisthoracies and iliocostalislumborum on patients with postural scoliosis than traditional physical therapy alone.

Competing interests

The authors declare that they have no competing interests.

References

1. Davies A, Saifuddin A. Imaging of painful scoliosis. Skeletal Radiol. 2009;(38):207–23.
2. Weinstein SL, Dolan LA, Cheng JC, Danielsson A, Morcuende JA. Adolescent idiopathic scoliosis. Lancet.
2008; (371): 1527–37.
3. Nault ML, Allard P, Hinse S, Le BR, Caron O. relations between standing stability and body posture parameters in adolescent idiopathic scoliosis. 2002; 27(17): 1911-7.
4. Ramirez N, Johnston CE, Browne RH. The prevalence of back pain in children who have idiopathic scoliosis. J Bone Joint Surg Am Mar. 19977; 9(3): 364-8.
5. Weinstein SL, Dolan LA, Spratt KF, Peterson KK, Spoonamore MJ, Ponseti IV. Health and function of patients with untreated scolioisis: A 50-year natural history. 2003; (289): 559-67.
6. Le BA, Brtalik R, Stow K. The effect of myofascial release (MFR) on an adult with idiopathic scoliosis. Journal of bodywork and movements therapies. 2008; (12): 356-63.
7. Kostopoulol D, Rizopoulos K. The manual of trigger point and myofascial therapy. Astoria, New York: Press; 2011. P. 3-4-7-10-14-64.
8. Paolini M, Bernitti A, Fratocchi G, Mangone M, Parenello M. Kinesio taping applied to lumber muscles influences clinical and electromyographic characteristics in chronic low back pain patients. European journal of physical and rehabilitation medicine. 2011; (47): 237-44.
9. Halseth T, McChesney JW, DeBeliso M, Vaughn R, Lien, J. The effects of Kinesio taping on proprioception at the ankle. Journal of Sports Science and Medicine. 2004;(3):1–7.
10. Kase K. Until today from birth of Kinesio taping method [in Japanese]. Albuquerque, NM: KMS, LLC. 2001;7–30.
11. Garcia D. Kinesio taping for the sense of balance on knee [in Japanese]. 16th-Annual Kinesio Taping International Symposium Review. 2001;20–3.
12. Otman S, Kose N, Yakut Y. The efficacy of Schroth's 3-dimensional exercise therapy in the treatment of adolescent idiopathic scoliosis in Turkey. Neurosciences Vol. 10. 2005;(4):277-83.
13. Fairbank and Pynsent. The Oswestry Disability Index. Spine. 2000; (25)22: 2940-53.
14. Merritt JL, Mclean TJ, Erickson RP, Offord KP. Measurement of trunk flexibility in normal subjects: reproducibility of three clinical methods. Mayo Clinic Proceedings. 1998; 61(3): 192-7.
15. Ebnezar J. Essentials of orthopedics for physiotherapists. 2nd edition by Jaypee Brothers (USA); Chap. 2011; 4: 288-93.
16. Castro-SA, Inmaculada C, Guillermo A, Manuel F, Nueria S, Manuel M. Kinesio taping reduces disability and pain slightly in chronic non-specific low back pain: a randomised trial. Journal of Physiotherapy. 2012; (58): 89-95.
17. Vorhies D. Testimonial of a Kinesio tape convert [in Japanese]. 15th AnnualKinesio Taping International Symposium Review. 1999; 122–3.
18. Deleo JA. Basic science of pain. Journal of bone and joint surgery American 88. 2006; (Suppl.2): 58-62.
19. Gonz´alez-IJ, Fern´CP, Cleland J, Huijbregts P, M Del RG. Short-term effects of cervical Kinesio taping on pain and cervical range of motion in patients with acute whiplash injury: a randomized clinical trial. Journal of Orthopaedic and SportsPhysical Therapy. 2009; 39(7): 515–21.
20. Marcin K, Bogacz K, Luniewski J, Jan S. The influence of Kinesio taping on the effects of physiotherapy in patients after laparoscopic cholecystectomy; The Scientific World Journal. 2012; 1- 5.
21. Garcia M, Rodriguez FAL, Herrero dLA. Treatment of myofascial pain in the shoulder with Kinesio taping. A case report. 2010; (15): 292-5.
22. Goo J. A new step for treatment of ankle sprain [in Japanese]. 16th Annual Kinesio Taping International Symposium Review. 2001; 16-9.
23. Roach JW. Adolescent idiopathic scoliosis: non-surgical treatement in: Weinstein SL, editor. The pediatric spine: principles and practice. New York: ravin press. 1997;497-510.
24. Negrini A, Negrini S. scoliosichinestrerapia e sport in: Cimino F, editor. La scoliosi in eta evolutiva: atuallita e technice di trattamento a confrontto. Modinaitaly: group kinesitherapiqueeuropeen de travilsur la scolios. 1991; (21): 1-21.
25. Cobb J. Outline for the study of scoliosis. In instructional course lectures Ann Arbor MI: American Academy for orthopedic surgeons. 1948; (5): 241-75.
26. Rainville J, Carol H, Eugenio M, Janet L. Exercise as a treatment for chronic low back pain. The spine journal. 2004; (4): 106-15.
27. Hansen FR, Bendex T, Skov P, Jensen CV, Kristensen, Krohn L, Schioeler H. Intensive, dynamic back- muscle exercises, conventional physiotherapy, or placebo controlled treatment of low back pain: a randomized, observer-blinded trial Spine. 1993; (8): 98-108.
28. Rissanen A, Kalimo H, Alaranta H. Effect of intensive training on the isokinetic strength and structure of lumber muscles in patients with chronic low back pain. 1995; 333-40.
29. Mayer TG, Smith S, Keeley J, Moony V. Quantification of lumber function part 2: sagittal plane trunk strength in chronic low back pain patients. 1985; 765-72.
30. Rainville J, Ahren DK, Phalen L, Childs LA. The association of pain with physical activities in chronic low back pain. 1992; 1060-4.
31. Estlander AM, Mellin G, Vanharanta H. Effects and follow up of a multimodal treatment program including intensive physical training for low back pain patients. Scand J Rehab Med. 1991; (23): 97-102.
32. Rie K. Current trends in exercise management for chronic low back pain: comparison between strengthening exercises and spinal segmental stabilization exercise. Journal of physical therapy sci. 2006; (18): 97-105.
33. Moffett JK, Torgerson D, Bell-SS, Jackson D, Llewlyn-Philips H, Farrin A, Barber J. Randomized controlled trial of exercise for low back pain: clinical outcomes, costs, and preferences. Br Med J. 1999; (319): 279-83.
34. Taimela S, Diederich C, Hubsch M, Heinricy M. The role of physical exercise and inactivity in pain recurrence and absenteeism from work after active outpatient rehabilitation for recurrent or chronic low back pain. 2000; (25): 1809-16.
35. Bendix T, Bendix A, Labriola M. Functional restoration versus outpatient physical training in chronic low back pain: a randomized comparative study. 2000; 2494-500.
36. Hansen FR, Bendex T, Skov P, Jensen CV, Kristensen JH, Krohn L, Schioeler H. Intensive, dynamic back- muscle exercises, conventional physiotherapy, or placebo controlled treatment of low back pain: a randomized, observer-blinded trial. Spine (Phila Pa 1976). 1993; 98-108.
37. Weinstein SL, Dolan LA, Change JC, Daielsson A, Morcuende JA. Adolescent idiopathic scoliosis. 2008; 371(3): 1527-37.
38. Ferraro C, Masiero S, Venturin A, Pigatto M. Effect of exercise therapy on mild idiopathic scoliosis. Europa Medico Physica. 1998; (34): 25-31.
39. Scheier H. Prognose und behandlung der skoliose. stuttgart: Theme. 1967; 48-91.
40. Lenssinck MLB, Frijlink AC, Berger My, Bierma-Zeinstra SMA, Verkerk K, Verhagen AP. Effect of bracing and other conservative interventions in the treatment of idiopathic scoliosis in adolescents: A systemic review of clinical trials. Phys Ther. 2005; (85): 1329 – 39.
41. Simon C, Harchad V. Efficacy of exercise therapy for the treatment of adolescent idiopathic scoliosis: a review of the literature. Euro Spine Journal. 2012; 21(3): 382-9.

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